JUL 10 1979
NCI/ICRDB/OB-78/03 MAR 30 1979
HE 20.3173/3:08-78/03
NTISUB/E/230-002

ONCOLOGY OVERVIEW

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ORIGINAL

SELECTED ABSTRACTS

ON

MURINE MAMMARY TUMOR VIRUSES

MARCH 6, 1979

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service • National Institutes of Health •
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TABLE OF CONTENTS

	ABSTRACT NUMBER
INTRODUCTION	
EDITORIAL COMMENTARY	
I. BIOCHEMICAL STUDIES OF THE MURINE MAMMARY TUMOR VIRUS (MuMTV)	
A. MuMTV Nucleic Acid Studies	1-25
B. Activities of the MuMTV RNA-Directed DNA Polymerase (RDDP) and Other Enzymes	26-46
C. Biochemical Studies of MuMTV Structural Components	47-67
II. GENERAL STUDIES ON THE DETECTION AND CHARACTERIZATION OF MuMTV	68-99
III. FACTORS INFLUENCING MuMTV EXPRESSION	
A. Hormonal Control of MuMTV Expression In Vitro	100-128
B. Hormonal Control of MuMTV Expression In Vivo	129-150
C. Other Factors Affecting MuMTV Expression	151-171
IV. GENETIC STUDIES OF MuMTV	172-183
V. IMMUNOLOGICAL STUDIES OF MuMTV	
A. Immunological Assay Procedures	184-191
B. Immunological Studies of MuMTV Antigenic Determinants	192-211
C. Autogenous Immunity to MuMTV and MuMTV-Induced Tumors	212-237
D. Alteration of Immunity to MuMTV and MuMTV-Induced Tumors	238-264
E. Alteration of Immunocompetence by MuMTV	265-269
F. Tumor Antigens Associated with MuMTV	270-281
VI. MAMMARY TUMORIGENESIS	
A. Occurrence and Growth of Spontaneous Mammary Tumors	282-301
B. Growth Control Studies of Transplanted Mammary Tumors	302-316
VII. STUDIES ON THE ASSOCIATION OF THE MuMTV AND HUMAN CANCER	
A. MuMTV and Human Cancer: Nucleic Acid Studies	317-329
B. MuMTV and Human Cancer: Enzyme and Protein Studies	330-333
C. MuMTV and Human Cancer: Immunological Studies	334-361
VIII. CULTIVATION AND CHARACTERIZATION OF MuMTV INFECTED CELL LINES	362-378
IX. CELL INFECTIVITY STUDIES OF MuMTV	379-393
X. MuMTV INTERFERENCE BY OTHER VIRUSES	394-397
XI. STUDIES OF INTRACYTOPLASMIC A-PARTICLES	398-409
XII. REVIEW ARTICLES	
A. General Review Articles	410-424
B. Reviews on the Association of MuMTV and Human Cancer	425-462
INDEX TO KEY WORDS IN TITLE	
AUTHOR INDEX	

INTRODUCTION

This ONCOLOGY OVERVIEW on murine mammary tumor viruses covers the publication years from 1970 to the most recent entries in the CANCERLINE data base. The strategy used for the on-line data base search is available on request from the CIDAC office and can be entered at any MEDLARS/MEDLINE terminal system in order to obtain continuing updates in this area.

The scope of this OVERVIEW covers the subject of the murine mammary tumor viruses, their biological, chemical, structural and immunological properties and investigations into the possible occurrence of similar viruses in humans.

This OVERVIEW was prepared by Dan Moore (Editor) at the Department of Microbiology and Immunology, Hahnemann Medical College and Hospital and Barbara Hindman of the CIDAC for Virology, Immunology and Biology, The Franklin Institute Research Laboratories.

EDITORIAL COMMENTARY

The period covered by this review is one of rapid growth in scientific interest in the murine mammary tumor virus (MuMTV) - one that probably equals that which occurred immediately after Bittner's discovery of the milk influence on mouse mammary tumorigenesis. Progress during the intervening years was hampered by slow and inadequate assay procedures and the inability to identify the milk agent. But by 1970, the acceptance of the B particle as the principal carrier of the bioactivity, the development of more rapid assay procedures and the discovery of important oncornaviruses in many species including cats, cattle, and primates, gave impetus to the study of RNA tumor viruses. The mammary tumor virus, however, held a special position in that it was both attractive and unattractive to investigators. It was attractive because it represented the only oncornavirus involved in the development of carcinomas, the type of cancer that occurs most frequently in humans, and it was unattractive because it was restricted to a single species, it had not been shown to infect cells in culture, and assay procedures were still time-consuming and cumbersome.

In the years 1970 to the present, outstanding advances in tumor virology were made, a few of which will be mentioned here. After years of recognition that DNA was somehow associated with Rous sarcoma virus replication, all previous notions of molecular biological translation of information were uprooted by the discovery of a polymerase contained in the virion that could translate information from RNA to DNA. This discovery had broad implications and greatly advanced our understanding of the oncogenic activity of the oncornaviruses. At about this time, it also was found that all mice of the species Mus musculus carried one or more copies of the MuMTV DNA genome in every cell, thus explaining why the incidence of mammary tumors could not be eradicated by removal of the milk agent through foster-nursing. All mice carry an endogenous MuMTV which can be latent or expressed to varing degrees.

Hormonal stimulation of pregnancy causes the endogenous virus to be expressed in some strains of mice but not in others. In some strains, it begins to be expressed after only one or two pregnancies (or in tissues even before pregnancy); in other strains, more stimulation is required to obtain secretion of virus in the milk. Usually, the virus removable from a mouse strain by foster-nursing is different from the endogenous virus of the same strain, although they are both infectious if suitable hosts are found.

Despite earlier failures, mice have now been shown to develop an immune response to MuMTV even though they may ingest the virus neonatally via the mother's milk. Neonatally infected mice, however, cannot be protected against tumor development by vaccination. Some low tumor strains can be protected by vaccination against later challenge with the same strain of virus that was used to make the vaccine. More sensitive techniques have been developed for detection of specific viral antigens as well as humoral antibodies and cellular immune responses to these antigens. Viruses from different mouse strains are now being examined for type-specific antigens. There is now the possibility of a much deeper understanding of the interaction between the host's immune system and viral antigens in the tumorigenic process.

Some aspects of the nature of the viral genome are not yet understood; e.g., the virus has an enigmatic resistance to ionizing irradiation, its tumorigenicity withstanding doses of gamma-ray irradiation of 4X10**6 R. Whether its infectivity is more sensitive to irradiation is not determined.

The protein components of the virus and their location in the virion have now been studied in considerable detail. The virion is composed of eleven or more polypeptides. Two of the five major ones are glycoproteins with molecular weights of about 52-55,000 (gp52) and 34,000 (gp34); the three major non-glycopeptides have molecular weights of about 28,000 (p28), 18,000 (p18), and 12,000 (p12). The former two, as well as some minor ones, are constituents of the outer membrane and the latter three plus minor ones are components of the viral core. In addition to the structural proteins, the virion contains the RNA-directed DNA polymerase (RDDP) with molecular weight of about 100,000 daltons.

During recent years, a great deal of effort has been expended in attempting to grow MuMTV in cell cultures. Cultures of tumor explants have provided established cell lines which have produced the virus in

varying amounts. Viral proliferation depends on the mouse strain from which the tumor cells are taken and also on the hormonal environment. Glucocorticoid steroids can greatly enhance MuMTV production by continuous cell lines synthesizing the virus. The virus produced in cultures has been shown to be infectious in mice, but has minor variances in structural components when compared with virions from milk.

A major handicap in investigations of MuMTV has been recently overcome by the succesful infection of cells in vitro. Lines of epithelial cells from cat, mink, buffalo rat, C57BL mice, and other species have been infected with several strains of the virus. The prospects for studying the infection process, the effect of hormones, and the process of transformation by MuMTV are now significantly enhanced because experiments can be carried out in a shorter time and in a much simpler system.

During this decade, an increased emphasis has been placed on the possible viral etiology of human breast cancer. Human milks and human tumors have been extensively scanned for the presence of virus or virus-related entities. RNA-directed DNA polymerase (RDDP) with some properties similar to that of the MuMTV RDDP has been obtained from particles isolated from many human milk samples; RNA from some human mammary tumors, but not other tissues, has been reported to hybridize to varying extents to probes prepared from MuMTV RNA; human-mouse virus cross-reacting antigens and antibodies have been found by several investigators; and occasionally, virus-like particles and even type-B particles have been seen in human milk preparations. Correlation of all these findings with the disease state has in general been poor, but as our understanding of tumor virology is improved, the role of viruses in the etiology of human cancer will be better evaluated.

I. BIOCHEMICAL STUDIES OF THE MURINE MAMMARY TUMOR VIRUS (MuMTV)

A. MuMTV Nucleic Acid Studies

1. ELECTRON MICROSCOPY OF THE NUCLEIC ACID OF MOUSE MAMMARY TUMOR VIRUS.

Sarkar NH, Moore DH
Inst. Med. Res., Camden, N. J.
J Virol; 5(2):230-236 1970

Mammary tumor virus (MTV) from the milk of RIII mice was purified by Ficoll density gradient centrifugation. The RNA was extracted with phenol and examined by electron microscopy. A histogram of the length distribution of 194 molecules showed distribution with a prominent peak between 1.1 and 1.3 microm (modal length; 1.2 microm). Another peak appeared at 2.4 microm. Since the max. RNA molecule length was observed to be 3.6 microm the overall modal length (1.2 microm) of the distribution is not likely to represent the length of an intact molecule; thus, it is probable that the length of an intact MTV-RNA molecule is 3.6 microm.

2. ISOLATION AND CHARACTERIZATION OF MOUSE MAMMARY TUMOR VIRUS CORES.

Teramoto YA, Cardiff RD
Dept. of Pathology, School of Medicine, Univ. of California, Davis, CA 95616
Proc Am Assoc Cancer Res; 16:133 1975

Subvirion particles of the mouse mammary tumor virus (MMTV) were isolated and analysed in order to further describe the structure of the MMTV virion. Treatment of purified MMTV virions (rho approximately or equal to 1.17g/cc) with various surfactants, followed by density gradient centrifugation, resulted in the separation of several particles with densities of 1.20 g/cc and greater. Electron microscopic examination of these isolated particles by negative stain and thin sectioning revealed structures which were morphologically similar to the nucleoid of intact virions. These particles had a limiting structural layer surrounding an electron dense central region, and lacked the spiked virion envelope. High molecular weight RNA and MMTV specific reverse transcriptase activity were localized within the high density particles. These particles, therefore, represent MMTV cores or core-like particles. SDS-PAGE showed that a 28,000 dalton polypeptide (p28) was consistently a major structural component of MMTV cores. Polypeptides of 14,000 and 30,000 daltons, along with variable amounts of minor polypeptides were also present. The major envelope glycoproteins were missing from such preparations. Immunological analyses identified p28 as the major antigen of the MMTV cores, and confirmed the absence of envelope antigens. The relationships among the core-like particles and their structural significance to MMTV virions will be discussed. (Author Abstract)

3. VISUALIZATION OF THE GENOMIC RNA FROM A B-TYPE TUMOR VIRUS (MEETING ABSTRACT).

Heine UI, Dion AS, Korb J, Ponenti A, Weber GH
National Cancer Institute, Bethesda, Md. 20014 and Institute for Medical Research, Camden, N.J. 08103
Proc Am Assoc Cancer Res; 17:104 1976

Genomic, high molecular weight RNA was isolated from a murine mammary tumor virus (MuMTV) derived from milk of RIII strain mice. After purification the RNA was found to have a molecular weight of 6 x 60^{6} after PAGE. Samples of the high molecular weight RNA were subjected to a modification of the Kleinschmidt Technique which allows visualization and examination of single-stranded nucleic acid molecules. The length of the MuMTV-RNA molecules was satisfactorily analyzed and our results show that molecules representing a molecular weight of 6 x 10^{6} are non-existent in our preparations whereas shorter molecules of about 3.4 .mu length are numerous. Their molecular weight was calculated to be 3 x 10^{6} using 28 S rRNA and the genomic RNA of a nononcogenic virus (vesicular stomatitis virus) as standards. The molecules of 3.4 .mu length represent subunit molecules being an integral part of the genomic oncornavirus RNA. It is postulated that two subunit molecules are corresponding to one molecule of the high molecular weight RNA of 60S or 6 x 10^{6} MW7 (Author Abstract)

4. ISOLATION OF THE MOUSE MAMMARY TUMOR VIRUS SEQUENCES NOT TRANSMITTED AS GERMINAL PROVIRUS IN THE C3H AND RIII MOUSE STRAINS.

Drohan W, Kettmann R, Colcher D, Schlom J
Meloy Lab, Springfield, Va 22151
J Virol; 21(3):986-995 1977

Radioactive 60-70S RNA from the mouse mammary tumor virus (MMTV) produced by the C3H mouse mammary tumor cell line (Mm5mt) hybridized to a greater extent, and at a lower C0t1/2 value, to the DNA of C3H mammary tumor cells than to the DNA of C3H liver cells. The ^{125}I-labeled MMTV(C3H) 60-70S RNA was annealed to a vast excess of DNA from C3H livers, and single-stranded RNA was eluted from hydroxylapatite and recovered. This "recycled RNA" did not hybridize to the DNA of the apparently normal organs tested from normal or from mammary tumor-bearing C3H mice, but hybridized extensively to both the DNA from the C3H mammary tumor cell line and the DNA from spontaneous C3H mammary tumors. This hybridization could be competed out by the addition of unlabeled MMTV 60-70S RNA but was unaffected by the addition of unlabeled 60-70S RNA of C3H type C virus. Similar experiments were conducted with the RIII mouse strain. We therefore report on the isolation of the sequences of the RNA genomes of the MMTVs from C3H and RIII mice that are transmitted by some mechanism other than via the germ line. These studies further define the differences, via molecular hybridization between the MMTV-S and the MMTV-L in both C3H and RIII mice. (30 Refs). (Author Abstract)

5. DIFFERENCES BETWEEN GENOMES OF TWO STRAINS OF MOUSE MAMMARY TUMOR VIRUS AS SHOWN BY PARTIAL RNA SEQUENCE ANALYSIS.

Friedrich R, Morris VL, Goodman HM, Bishop JM, Varmus HE
Dept. Microbiology, Univ. California, San Francisco, CA 94143

Virology; 72(2):330-340 1976

The nucleotide sequences of two biologically distinct strains of mouse mammary tumor virus, MMTV-S and MMTV-P, were studied. ^{32} P-labeled viral 70S RNA was digested with RNAse T1, and the resultant oligonucleotide products were separated by two-dimensional electrophoresis and displacement chromatography (homochromatography). The resultant patterns showed both similarities and differences in the positions of large oligonucleotides. The large T1 - resistant oligonucleotides were analyzed by RNAse A digestion and paper electrophoresis, revealing similarities and differences in the composition of oligonucleotides derived from the genomes of the two viral strains. The genomic complexity of both viruses was calculated to be approx 3×10^6 daltons. This complexity together with the estimated molecular weight of the 70S RNA suggests that the genomes from these viruses are polyploid. (38 refs)

6. NUCLEOTIDE SEQUENCE HOMOLOGIES AMONG MOUSE MAMMARY TUMOR VIRUSES.

Ringold GM, Blair PB, Bishop JM, Varmus HE
Dept. Microbiology, Univ. California, San Francisco, CA 94143

Virology; 70(2):550-553 1976

Competition hybridizations were performed to determine the nucleotide sequence homology among the genomes of several mouse mammary tumor viruses (MMTV). DNA was made complementary to the entire genome of MMTV produced by GR tumor cells (MMTV-P), and the ability of RNAs from other virus strains (MMTV-L and MMTV-S) to compete with labeled RNA from MMTV-P for annealing to this DNA was tested. RNA from these strains was found to compete with 96-100% of labeled RNA from MMTV-P, indicating that the genomes of MMTV viruses are composed of closely related nucleotide sequences.

7. A BIOCHEMICAL APPROACH TO THE STUDY OF THE TRANSMISSION OF MOUSE MAMMARY TUMOR VIRUSES IN MOUSE STRAINS RIII AND C3H.

Michalides R, Vlahakis G, Schlom J
Meloy Laboratories, Springfield, VA 22151

Int J Cancer; 18(1):105-115 1976

Mouse mammary tumor virus (MMTV) proviral sequences were detected in the cellular DNA of mammary tumors and livers of RIII and C3H mice by molecular hybridization with radioactively labelled MMTV 60-70S RNA or tritiated MMTV complementary DNA (cDNA). By means of DNA:DNA reassociation kinetics, the DNA of the mammary tumor cells of these two mouse strains were found to contain more MMTV proviral sequences than the DNA of liver cells of these same tumor-bearing mice. Evidence is also presented that the DNA of the liver cells lacks a part (approximately 25%) of the MMTV proviral sequences found in the mammary tumor cells of these mouse strains. The relationship of the extra MMTV proviral sequences found in mammary tumor cells to the early mammary tumorigenesis seen in these mouse strains is discussed. (Author Abstract)

8. RELATIONSHIP IN NUCLEIC ACID SEQUENCES BETWEEN MOUSE MAMMARY TUMOR VIRUS VARIANTS.

Michalides R, Schlom J
Meloy Laboratories, Inc., Springfield, Virginia 22151; and National Cancer Institute, National Institutes of Health, Bethesda, MD 20014

Proc Natl Acad Sci USA; 72(11):4635-4639 1975

Primary cultures of mouse mammary carcinomas were used as a source of both radioactively labeled and unlabeled 60-70S RNA of mouse mammary tumor virus (MMTV) obtained from various mouse strains. Competition molecular hybridization experiments revealed that, within the limits of the assay, the RNAs of the MMTVs synthesized in culture by the tumors of the mouse strains RII, GR, A, and C3H, are identical. A comparison of the genomes of the milk-transmitted MMTV(C3H) and the vertically transmitted MMTV(C3H) revealed that these two viruses are approximately 75% similar. No nucleic acid sequence homology was observed between MMTV(C3H) 60-70S RNA and the RNAs of murine leukemia virus, Mason-Pfizer virus, or the BrdUrd-induced type-B guinea pig virus. (Author Abstract)

9. A COMPARATIVE STUDY OF THE BIOLOGIC AND MOLECULAR BASIS OF MURINE MAMMARY CARCINOMA: A MODEL FOR HUMAN BREAST CANCER.

Schlom J, Michalides R, Kufe D, Hehlmann R, Spiegelman S, Bentvelzen P, Hageman P
Columbia U. Coll. Physicians Surgeons, New York, N.Y.

J Natl Cancer Inst; 51(2):541-551 1973

The technique of molecular hybridization was used in a comparative study of the molecular and biological basis of murine mammary neoplasia as a model for the human disease. 3H-DNA complementary to mouse mammary tumor virus (MMTV) RNA was synthesized in an endogenous reaction with MMTV particles. This DNA was used as a probe via molecular hybridization to establish the presence of MMTV-specific RNA in cellular RNA of "spontaneous" mammary tumors of several strains of mice, including the "nonproducer" BALB/c mammary tumors. Hybridization of MMTV-3H-DNA to cellular RNA in these tests was scored as "positive" or "negative" according to amounts of 3H-DNA hybridized to the larger cellular RNA molecules. MMTV-specific RNA was also found in certain normal tissues (spleen, kidney, and epididymis) of a high-mammary-cancer strain (GR). Aging or treatment with nonviral carcinogens (300 rads irradiation or 0.15% urethane in drinking water) also induced the appearance of MMTV-specific RNA in certain normal tissues of the low-mammary-cancer strains, C57BL and BALB/c. The relationship of the presence of MMTV-specific RNA to the etiology and pathogenesis of murine mammary neoplasia and its potential application to human breast cancer are discussed.

10. EVIDENCE FOR TRANSLATION OF VIRAL-SPECIFIC RNA IN CELLS OF A MOUSE MAMMARY CARCINOMA (MEETING ABSTRACT).

Axel R, Schlom J, Spiegelman S
Coll. Phys. Surg., Columbia U., New York, N.Y.

Proc Natl Acad Sci USA; 69(3):535-538 1972

A procedure for detection of viral-specific RNA in a mouse mammary tumor is described. 3H-labeled DNA synthesized in vitro for murine mammary tumor virus RNA templates, purified from viruses found in the milk of tumor-bearing Paris RIII strain mice, was used to test for the presence of RNA homologous to viral RNA in nuclear and polysomal fractions of breast tumors from Paris RIII mice, and of normal breast tissue from lactating tumor-free C57 mice. The purified 3H-dTTP-labeled denatured DNA was

annealed (0.4 M NaCl -50% formamide, 18hr at 37 C) to nuclear or polysomal RNA preparations from tumor tissue, and analyzed by Cs2SO4 equilibrium density gradient centrifugation. Both preparations were found to contain RNA molecules complementary to the 3H-DNA from mammary tumor virus with 30-35% of 3H-DNA shifting to regions of the gradient corresponding to hybrid density. Polysomal RNA from normal mouse liver did not hybridize with mammary-tumor viral 3H-DNA nor did breast tumor polysomal RNA complex with 3H-DNA homologous to the RNA of Rauscher leukemia virus, on oncogenic agent unrelated to the mouse mammary tumor virus. Polysomal RNA from normal breast also showed no ability to hybridize to tumor virus 3H-DNA. The reaction between breast-tumor polysomal RNA and viral DNA was therefore concluded to be specific. Hybridization reactions using 3H-DNA from tumor virus and purified monosomal or polysomal RNA from mammary tumor indicated that breast-tumor RNA hybridizable to viral DNA was in the polysomes. The results implied that the oncogenic information was serving as messenger RNA to direct synthesis of proteins required for virus production, and perhaps for the maintenance of the neoplastic state as well.

11. MAMMARY TUMOUR VIRUS SPECIFIC NUCLEOTIDE SEQUENCES IN MOUSE DNA.

Varmus HE, Bishop JM, Nowinski RC, Sarkar NH
San Francisco Med. Ctr., Calif.
Nature New Biol; 238(34):189-191 1972

Mammary tumor virus (MTV) DNA was extracted from virus isolated from RIII mouse milk and single and double stranded DNAs were separated by batch elutions from hydroxyapatite powder. Sixty-five percent of the DNA eluted as double stranded material, but when the DNA was denatured and reassociated, only 50% reformed as duplexes. About half the reannealed DNA hybridized with MTV 70S RNA. The remaining DNA showed reassociation kinetics like those of double stranded Rous sarcoma virus and murine leukemia virus DNA. Double stranded MTV DNA was used as a probe for virus-specific nucleotide sequences in DNA from GR and C57BL/6 mouse liver cells and from virus-producing nontumorous mammary tissue of GR mice. DNA from liver cells accelerated the annealing rate of MTV double stranded DNA, indicating that about 90 copies of the MTV sequence were present per diploid liver cell.

12. IDENTIFICATION OF THE NUCLEIC ACID OF MOUSE MAMMARY TUMOR VIRUS (MTV) USING FLUORESCENCE MICROSCOPY.

El-Fiky SM, Sarkar NH, Moore DH
Med. Res. Inst. Alexandria, United Arab Republic
Acta Histochem (Jena); 37(2):323-329 1970

The specificity of the acridine orange staining technique used for identification of RNA of the mouse mammary tumor virus has been tested by fluorescence microscopy. Dried droplet preparations of concentrated virions of Rauscher murine leukemia, influenza, mammary tumor virus and nucleoids of mammary tumor virus fluoresced a flame-red in blue-violet light while smears of reovirus showed a yellow-green fluorescence, indicating a double-stranded RNA; vaccinia virus preparations showed brilliant apple-green fluorescence indicating also the presence of double-stranded DNA. After nuclease digestion (RNase, DNase) as well as digestion with 0.5% pepsin,no change in fluorescence of B particles was observed, but treatment with pepsin, trypsin and deoxyribonuclease resulted in pale orange fluorescence. After treatment with the proteolytic enzymes and ribonuclease, the B particles were readily susceptible to ribonuclease action and showed green fluorescence; following incubation either with pepsin or ribonuclease, the fluorescence was flame-red. Following staining with acridine orange, the nucleoid fraction of P particles gave flame-red fluorescence, while the membrane fraction fluoresced green. These results provide convincing evidence for the single-stranded nature of the mammary tumor virus RNA in confirmation of earlier reports.

13. ANALYSIS OF THE TRANSFER RNA POPULATION OF MOUSE MAMMARY GLANDS INFECTED WITH A LATENT MAMMARY TUMOR VIRUS.

Hentzen D
Electro-Radiologie, U.E.R. Medicate, Universite Louis Pasteur, Strasbourg, France
Cancer Res; 36(9):3082-3085 1976

Mammary gland transfer RNA's (tRNA's) of C3H mice infected with mammary tumor virus were analyzed in the preneoplastic state and compared to tRNA's of virus-free C3Hf mice and another uninfected strain, C57BL/6, which is completely resistant to cancer. This quantitative study was based on the ability of each tRNA to fix its corresponding amino acid. The amount of each of the 17 tRNA's tested was identical for the three mammary glands. In addition, tRNA populations during lactation correlated with the amino acids incorporated into the lactoproteins synthesized, which indicates adaptation of the tRNA's to protein biosynthesis. Qualitative chromatographic studies on reverse phase capillary columns Type 5 to 10 aminoacyl-tRNA's did not reveal any difference in the isoacceptor elution profiles. This shows that no new isoaccepting tRNA is associated with the mammary tumor virus at that stage, and that no viral modification of a host tRNA has occurred. (Author Abstract)

14. LEVELS OF MMTV SEQUENCES IN DNA OF "VIRUS-" AND "HORMONE-INDUCED" MALIGNANT MAMMARY EPITHELIAL CELLS OF THE BALB/C MOUSE (MEETING ABSTRACT).

McGrath CM, Marineau EJ, Voyles BA
Dept. of Biology, Michigan Cancer Foundation, Detroit, MI 48201
Proc Am Assoc Cancer Res; 18:245 1977

The alveolar stem cell of mammary parenchyma in BALB/c females is susceptible to transformation by exogenous mammary tumor viruses (MMTV-Ex) and by exogenous hormones (MTH). These normal cells also contain an endogenous MMTV variant (MMTV-En) in DNA. This study was designed to determine if MMTV-Ex and MTH acting as environmental carcinogens, exerted an effect on normal stem cells to alter MMTV information contained in nuclear DNA. Hybridization kinetics experiments using MMTV cDNA show that each normal alveolar cell contains 3-4 copies of MMTV-En information in DNA. Malignant alveolar cells transformed by MMTV-Ex contain 6-8 copies in DNA. Results of saturation hybridization experiments using DNA from cloned cells suggests that "extra" MMTV sequences detected in malignant cells are present in normal cells at low frequency. MMTV sequence amplification also does not change MMTV information present in normal cell DNA. MMTV-En sequences are not amplified in DNA of alveolar cells transformed by MTH. This suggests that while MMTV sequence amplication is not merely the result of malignant alveolar cell proliferation, neither is the process necessary for cell transformation. (Author Abstract)

15. THE PRESENCE AND EXPRESSION OF RNA TUMOR VIRUS GENES IN NORMAL AND INFECTED CELLS: DETECTION BY MOLECULAR HYBRIDIZATION.

Bishop JM, Jackson N, Levinson WE, Medeiros E, Quintrell N, Varmus HE
Dept. Microbiol., U. of California, San Francisco
Am J Clin Pathol; 60(1):31-43 1973

Three molecular probes were used to detect genes of the Rous sarcoma virus and mouse mammary tumor virus in normal and infected cells. Using the 70S RNA of the viral genomes and the single- and double-stranded DNA transcribed from viral RNA by RNA-directed DNA polymerase, it was found that multiple copies of viral genes may be present in the DNA of ostensibly normal cells. However, the infection and transformation of mammalian (mouse and rat) cells by Rous sarcoma virus is accompanied by the appearance of virus-specific nucleotide sequences in the nuclear DNA of the host cells. The expression of Rous sarcoma virus and mouse mammary tumor virus genes in normal and infected cells was measured by RNA-DNA hybridization. Virus-specific RNA is present in both normal and transformed cells which produce neither virus nor detectable viral proteins. These data indicate that the expression of viral genes may not be controlled exclusively by the regulation of transcription.

16. DNA SYNTHESIS BY RNA-CONTAINING TUMOR VIRUSES (MEETING ABSTRACT).

Scolnick EM, Aaronson SA, Todaro GJ
Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.
Proc Natl Acad Sci USA; 67(2):1034-1041 1970

The occurrence of an RNA -dependent DNA polymerase and some characteristics of the polymerase reaction (kinetics, sedimentation and activity) were studied in oncogenic and non-oncogenic RNA viruses. The in vitro DNA polymerase required the 4 essential deoxyribonucleoside triphophates; the reaction was dependent on temperature (optimal activity at 37 C), and optimal DNA synthesis occurred with Triton X-100 concentration at 0.010-0.014% for Rauscher leukemia virus and Moloney leukemia virus. In a sucrose gradient virion, enzymatic activity and the DNA product that was synthesized cosedimented, suggesting that the 3 are part of a ternary complex. In the DNA polymerase assay, the rate of incorporation (cpm) varied greatly among individual viruses with Rauscher leukemia virus the most active (64,000 compared to its control 430 with only 3 of the 4 essential nucleotides in the reaction). Other viruses showing activity were Moloney leukemia virus (5,900 compared to its control 401), Rauscher leukemia virus grown in human cells (2,000 compared to 295), Kirsten sarcoma virus (1,050 compared to 350), and a mammary tumor virus (1, 050 compared to 301). The non-oncogenic RNA viruses (Sendai, respiratory syncytial, Newcastle disease, lymphocytic choriomeningitis, and influenza viruses) were inactive.

17. REPLICATION OF MOUSE MAMMARY TUMOR VIRUS IN TISSUE CULTURE. II. KINETICS OF VIRUS PRODUCTION AND THE EFFECT OF RNA AND PROTEIN INHIBITORS ON VIRAL SYNTHESIS.

Sarkar NH, Pomenti AA, Dion AS
Memorial Sloan-Kettering Cancer Center, 1275 York Ave. New York, NY 10021
Virology; 77(1):31-44 1977

An analysis of RNA species in purified mouse mammary tumor virus (MuMTV) derived from cultured mouse mammary tumor cells (MuMT-73) showed that the virions harvested soon after the addition of ^{3}H-uridine contained 65S-70S, 42S, 30S-35S, 20S-22S, and 4S RNA's. The 70S and 35S species of RNA were found to be virus-specific by molecular hybridization using radioactive MuMTV-complementary DNA as a probe. Two to 4 hr lapsed between the addition of ^{3}H-uridine and the initial release of virions containing labeled 70S and 35S. Incubation of the cells with actinomycin D completely inhibited viral RNA synthesis within 1 hr, whereas synthesis of viral proteins and the release of mature virions continued for at least 10 hr. The protein composition and architecture of the virus particles produced by the treated and untreated MuMT-73 cells were identical. Exposure of cells to puromycin or cyclohexamide inhibited the replication of MuMTV, but induced the production of an endogenous C-type virus. (35 Refs)

18. POSSIBILITY OF A DNA-CONTAINING MAMMARY TUMOUR VIRUS IN RED BLOOD CELLS OF MOUSE.

Nandi S
Dept. Zool., U. California, Berkeley
Nature (Lond); 230(13):146-147 1971

The RBC fraction was separated from the blood of 6-8 wk old BALB/cfC3H mice infected with mammary tumor virus and incubated with various proteases and nucleases for 2 hr at 37 degrees either singly or in combination. Neither proteases nor nucleases were able to destroy the infectivity of the RBC fraction; however, the addition of RNase or DNase following treatment with protease caused complete inactivation. However, when DNase or RNase was previously treated with a nuclease inhibitor, the effect was lost. These results demonstrate the nucleoprotein nature of the infective moiety designated as R-MTV.

19. PURIFICATION OF DNA COMPLEMENTARY TO NUCLEOTIDE SEQUENCES REQUIRED FOR NEOPLASTIC TRANSFORMATION OF FIBROBLASTS BY AVIAN SARCOMA VIRUSES.

Stehelin D, Guntaka RV, Varmus HE, Bishop JM
I.R.S.C., B.P. 8, 94800-Villejuif, France
J Mol Biol; 101(3):349-365 1976

Radioactive DNA complementary to nucleotide sequences representing a portion of the viral gene(s) required for transformation of fibroblasts (cDNA-sarc) by avian sarcoma virus (ASV) was prepared. In addition, some physical and chemical properties of cDNA sarc are presented, and the distribution of nucleotide sequences homologous to cDNA sarc among various RNA tumor virus strains is explored. Single-stranded DNA complementary to the AS virus genome was annealed to 70S RNA from a transformation-defective variant; the DNA that failed to anneal, representing viral nucleotide sequences absent from the genome of the deletion mutant, was separated from RNA/DNA hybrids by chromatography on hydroxylapatite with a shallow gradient of sodium phosphate and supplemented with 0.6 M NaCl to stabilize the RNA/DNA hybrids. cDNA sarc was a relatively uniform transcript from 16% of the nucleotide sequences in the genome of Prague strain-subgroup C ASV, and its genetic complexity was about 1,600 nucleotides, sufficient to represent an entire cistron. The genomes of three independent isolates of AS viruses shared nucleotide sequences closely related to cDNA sarc, whereas the sequences were absent from transformation-defective mutants of ASV, several avian leukemia viruses, a nonpathogenic endogenous virus of chickens (Rous-associated virus-O), sarcoma-leukosis viruses of mice and cats, and mouse mammary tumor virus. The authors conclude that the transforming gene(s) of all ASV have closely related or common genetic lineages distinct from the transforming genes in sarcoma viruses of other species. The results confirm previous reports that the transformation-defective variants of AS viruses are mutants with identical regions deleted from each subunit of a polyploid genome. (41 refs)

20. PRIMATE AND MURINE TYPE-C VIRAL NUCLEIC ACID ASSOCIATION KINETICS: ANALYSIS OF MODEL SYSTEMS AND NATURAL TISSUES.

Scolnick EM, Parks W, Kawakami T, Kohne D, Okabe H, Gilden R, Hatanaka M

Natl. Cancer Inst., Bethesda, MD

J Virol; 13(2):363-369 1974

The single-stranded 3H-DNA transcript of the type-C viruses isolated from the woolly monkey and gibbon ape were used in hybridization studies to investigate the distribution of these viruses in primates. The results were compared with those obtained in studies in which type-B and type-C viruses in mice were employed as model systems. The 3H-DNA transcript from RIII mouse mammary tumor virus (M-MTV) (type-B virus) and the Kirsten strain of murine type-C virus (Ki-MuLV) RNAs hybridized readily to all mouse tissue DNAs examined, including L8A clone 11 DNA, BALB/c 3T3 DNA, NIH 3T3 DNA, and DNA derived from a fetal mouse cell culture line. Nonmurine DNAs from rat, human, and calf thymus gave no detectable hybridization with the murine type-B and C 3H-DNA transcriptions. Sheared DNA from human cells infected with woolly monkey type-C virus or gibbon type-C virus readily hybridized to the woolly monkey viral 3H-DNA probe, while clinically normal woolly monkey, gibbon, marmoset, rhesus, African green monkey, chimpanzee, and human acute lymphoblastic and myelocytic leukemic DNAs failed to hybridize to the radioactive probe. Rat cellular DNA and calf thymus DNA also failed to hybridize significantly with the transcription. The woolly monkey sarcoma genome present in the HT-1 type of nonproducer rat cells contained nucleic acid sequences homologous to the woolly monkey helper virus, and the 3H-DNA transcript used detected the sequence in the DNA of such cells. The gibbon type-C virus 3H-DNA probe readily hybridized to DNA from cells infected with gibbon virus and the 60-70S RNA prepared from the gibbon virus, but failed to give appreciable hybridization to uninfected gibbon liver DNA, DNA from human placenta, fresh ALL and AML cells, cells from rat, rabbit, or guinea pig liver. It is possible that all primate cells do not contain complete copies of the C-type viruses, or, alternatively, that the viruses thus far isolated from the woolly monkey and gibbon ape may have originated in another species and seldom if ever undergo vertical transmission in primates.

21. THE RELATIONSHIP OF VISNA, MAEDI AND RNA TUMOR VIRUSES AS STUDIED BY MOLECULAR HYBRIDIZATION.

Harter DH, Axel R, Burny A, Gulati S, Scholm J, Spiegelman S

Coll. Physicians, Surgeons, Columbia U., New York, N.Y.

Virology; 52(1):287-291 1973

The relationship of visna and maedi viruses was investigated in experiments designed to determine if nucleic acid sequence homology could be demonstrated by molecular hybridization. Studies were also made to determine if hybridization could be demonstrated between visna and maedi virus nucleic acids and the nucleic acids of representative mammalian RNA tumor viruses. The DNA product of the endogenous visna virus RNA-directed polymerase reaction annealed to maedi virus 60-70S RNA. Similarly, the DNA product of the endogenous maedi virus polymerase reaction hybridized to visna virus 60-70S RNA. The DNA products of endogenous visna and maedi virus polymerase reactions failed to anneal significantly either to Rauscher murine leukemia or mouse mammary tumor virus 60-70S RNAs. The results indicate that visna virus and maedi virus have homologous nucleic acid sequences.

22. HELICAL NUCLEOCAPSID STRUCTURE OF THE ONCOGENIC RIBONUCLEIC ACID VIRUSES (ONCORNAVIRUSES).

Sarkar NH, Nowinski RC, Moore DH

Inst. Med. Res., Camden, N.J.

J Virol; 8(4):564-572 1971

The internal structures of avian myeloblastosis virus (AvLV), murine leukemia virus (MuLV), murine mammary tumor virus (MTV) and feline leukemia virus (FeLV) as demonstrated by negative straining techniques have several characteristics in common. Some virions penetrated by phosphotungstic acid showed spherical nucleoids with subunit structures composed of strands of nucleoprotein about three nm in diameter arranged in a double helix seven to nine nm in diameter. Most virions, however, had spherical nucleoids with no apparent symmetry. It was postulated that the nucleocapsid of a freshly-budded virus was supercoiled as a hollow sphere. Release of the virus into the extracellular space resulted in uncoiling of the helical nucleocapsid, due to changes in the microenvironment, with subsequent formation of a condensed nucleoid. This resulted in a random arrangement of the nucleoprotein strands. These strands coalesced during formation of the B particle thus leaving the nucleoid capsule visible. Such coalescence did not occur in formation of the C particle. Thus, the extracellular virion was considered a degenerate form with respect to nucleocapsid structure which explained the fact that helical nucleocapsids were rarely seen in RNA tumor viruses.

23. DNA AND THE RNA VIRUSES (MEETING ABSTRACT).

Spiegelman S

Coll. Phys. Surgeons, Columbia U., New York City, NY

Proc R Soc Lond Biol; 177(1046):87-108 1971

Incorporation of tritium-labeled thymidine triphosphate into acid-insoluble products were observed with serial transfer preparation of Rous sarcoma virus, Rauscher leukemia virus, feline leukemia virus, avian myeloblastosis virus, Moloney sarcoma virus, murine and monkey tumor viruses. Rous sarcoma virus and Rauscher leukemia virus DNA polymerases maintained linear synthesis for time periods extending to 8 hr, whereas the avian myeloblastosis virus, feline leukemia virus and murine mammary tumor virus polymerases showed a tendency to slow down after about 90 min. Preparations which did not require pretreatment with detergent to exhibit activity were severely inhibited by the 0.2% detergent required to disrupt the virions. The acid-precipitable product was degraded by DNAse but not by RNAse, pronase or sodium hydroxide and had a density within the DNA range of 1.450. Results of an annealing reaction between 3H-labeled DNA synthesized with the Rauscher leukemia virus polymerase and a great excess of RNA purified from the virions showed that all the DNA synthesized by the polymerase had some complementarity to the viral RNA. Intermediates of the polymerase reaction isolated after 20 min were found to be DNA-RNA hybrids.

24. SYNTHETIC DNA-RNA HYBRIDS AND RNA-RNA DUPLEXES AS TEMPLATES FOR THE POLYMERASES OF THE ONCOGENIC RNA VIRUSES.

Spiegelman S, Burny A, Das MR, Keydar J, Schlom J, Travnicek M, Watson K

Inst. Cancer Res., Columbia U., New York, N.Y.

Nature (Lond); 228(5270):430-432 1970

Polymerase activity of 6 oncogenic RNA viruses was studied by using synthetic polynucleotides as templates. Analysis of the responses of avian myeloblastosis virus (AMV), feline leukemia virus (FLV), Moloney sarcoma virus (MSV), Rauscher leukemia virus (RLV), mouse mammary

tumor virus (MTV), and a rat mammary tumor virus (RMTV) to resident RNA templates, to exogenous DNA (from trypsinized chick embryo cells), and to a synthetic hybrid duplex (dC.rG) indicated that the hybrid directed DNA synthesis ranged from 12 times to 351 times higher than the RNA or DNA directed syntheses. Among the ribohomopolymers, only rC possessed detectable template activity (pmoles nucleotide incorporated/5 min/10 microg viral protein) for AMV-polymerase (3.8), and among deoxyribopolymers, poly dC (11.0), poly dA (1.2), and poly dI (1.2) showed template activity. Except for rC.rG, all the synthetic double-stranded RNA and DNA homopolymers stimulated some incorporation of the complementary nucleotide pairs (the polyribopolymers appeared more effective than the corresponding deoxypolymers except for rC-.rG). Some of the synthetic DNA-RNA hybrid duplexes, particularly dC.rG and dI.rC (141.0 and 104.6, resp), were the most effective templates studied.

25. MASON-PFIZER VIRUS RNA GENOME: RELATIONSHIP TO THE RNA OF MORPHOLOGICALLY SIMILAR ISOLATES AND OTHER ONCORNAVIRUSES.

Colcher D, Drohan W, Schlom J
Meloy Laboratories, Inc., Springfield, Virginia 22151
J Virol; 17(3):705-712 1976

The 60-70S RNA of Mason-Pfizer virus (MPV) was iodinated in vitro and used in both direct and competitive molecular hybridization studies. MPV provirus sequences are present at a frequency of approximately one to two copies per haploid genome in the DNA of experimentally infected human cells. By nucleic acid competition hybridization, MPV RNA was found to be indistinguishable from the RNA of a virus (X381) isolated from a rhesus mammary gland and from RNA isolated from the cytoplasm of AO cells (Parks et al, 1973) and HeLa cells (Gelderblom et al, 1974), both previously reported to produce MPV-related particles. No homology was observed, however, between MPV RNA and the RNA, or the DNA, from two clones of HeLa cells obtained from the American Type Culture Collection. Hybridization of MPV 60-70S RNA to the DNA of normal tissues of humans and to the DNA of 11 other species revealed that MPV is not an endogenous virus of any of these species. Competition hybridization revealed no detectable sequence homology between the RNA of MPV and the RNAs of simian sarcoma virus, murine mammary tumor virus, murine leukemia virus, BUdR-induced guinea pig virus, or avian myeloblastosis virus. These nucleic acid studies substantiate previous ultrastructural and immunological findings that MPV and morphologically similar isolates constitute a distinct group of oncornavirus.

B. Activities of the MuMTV RNA-Directed DNA Polymerase (RDDP) and Other Enzymes

26. VIRAL RNA-DEPENDENT DNA POLYMERASE.

Baltimore D, Temin HM, Mizutani S
Dept. Biology, Massachusetts Inst. Technology Cambridge, MA 02139
Nature; 226:1209-1213 1970

Two independent groups of investigators have found evidence of an enzyme in virions of RNA tumor viruses which synthesizes DNA from an RNA template. This discovery, if upheld, will have important implications not only for carcinogenesis by RNA viruses but also for the general understanding of genetic transcription: apparently the classical process of information transfer from DNA to RNA can be inverted. (Author abstract) (37 Refs)

27. PURIFICATION AND PROPERTIES OF MURINE MAMMARY TUMOR VIRUS DNA POLYMERASE

Marcus SL, Sarkar NH, Modak MJ
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY
Virology; 71(1):242-254 1976

Murine mammary tumor virus (MuMTV) DNA polymerase was purified by affinity chromatography on polycytidylate-agarose followed by phosphocellulose ion-exchange chromatography. The resulting enzyme preparation contained two major polypeptides of 85,000 and 50,000 daltons as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, and appeared, except for low levels of ribonuclease (RNase)H, free of deoxyribonuclease and RNase activity. The molecular weight of the purified native enzyme, as determined by velocity sedimentation, was approximately 108,000. MuMTV DNA polymerase appears to be a zinc metalloenzyme and requires at least one reduced sulfhydryl group for the expression of catalytic activity. Apparent Km values determined for synthetic template-primers and deoxynucleoside triphosphates were 1 ug/ml and 10-12 uM, respectively. Examination of the optimal biochemical conditions for DNA synthesis on a variety of template-primers revealed that Mg2+ I was the preferred divalent cation for DNA synthesis. Mn2+ I could partially substitute for Mg2+ I, although it inhibited DNA synthesis when added in the presence of Mg2+ I. MuMTV DNA polymerase exhibited a preference for (dC)n.(dG)12-18 among all the synthetic template-primers tested. Activated DNA was preferred as a heteropolymeric template for DNA synthesis when compared with viral 70S RNA with either endogenous primers or with (dT)10 as a primer. Rates of heat inactivation of the MuMTV DNA polymerase varied according to the template-primer used.

28. RNASE H AND RNA-DIRECTED DNA POLYMERASE: ASSOCIATED ENZYMATIC ACTIVITIES OF MURINE MAMMARY TUMOR VIRUS.

Dion AS, Williams CJ, Moore DH
Inst for Medical Res, Camden, NJ 08103
J Virol; 22(1):187-193 1977

The RNA-directed DNA polymerase of murine mammary tumor virus, a type B RNA tumor virus, was purified sequentially through DEAE-cellulose, phosphocellulose (step gradient), and phosphocellulose (linear salt gradient) chromatography followed by glycerol sedimentation centrifugation. During all stages of purification, coincident peaks of RNA-directed DNA polymerase activity, templated by polyribocytidylate oligodeoxyguanidylate, and RNase H digestion of (^{3}H)polyriboadenylate-polydeoxythymidylate were observed, and both enzymatic activities displayed a cation preference for magnesium. Under conditions that removed adventitiously associated nucleases, RNase H activity was found to co-purify with polymerase. The specificity of this nuclease was assayed with various prepared substrates, which indicated that the polymerase-associated RNase H activity was directed only against the RNA strand of an RNA-DNA hybrid. It is highly probable that RNase H (RNA-DNA hybrid: ribonucleotidehydrolase, EC 3.1.4.34) and RNA-directed DNA polymerase of type B viruses are associated enzymatic activities analogous to those observed for avian and mammalian type C RNA tumor viruses. (19 Refs). (Author Abstract)

29. CHARACTERIZATION OF A TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE ACTIVITY IN MOUSE MAMMARY TUMOR VIRUS.

Ashley RL, Cardiff RD, Manning JS
Dept. Pathology, Sch. Medicine, Univ. California, Davis, CA 95616
Virology; 77(1):367-375 1977

Mouse mammary tumor virus (MMTV) contains a DNA polymerase that acts without template direction. This enzyme catalyzes the incorporation of deoxynucleoside monophosphates into an acid-precipitable product in the presence of a preformed initiator and is characteristic of terminal deoxynucleotidyl transferases (TdT). Optimal reaction conditions include pH of 6.85 and the use of a thymidine-containing substance and initiator. Terminal transferase activity was found to be associated with both the MMTV virions and cores. Manipulation of optimal conditions established a functional separation of RNA-dependent DNA polymerase (RDDP) and TdT. S1 nuclease digestion revealed that most of the TdT reaction product was single-stranded. Terminal transferase does not require exogenous template instruction, but endogenous poly(A) could have a template function in this reaction. (25 Refs)

30. MOUSE MAMMARY TUMOR VIRUS DNA POLYMERASE: PURIFICATION AND PROPERTIES (MEETING ABSTRACT).

Marcus SL, Sarkar NH, Modak MJ
No affiliation given
J Cell Biol ; 67(2/Part2):258a 1975

The DNA polymerase from mouse mammary tumor virus (MMTV) was purified using affinity chromatography on polycytidylate-agarose. The active enzyme was found to possess a molecular weight of 100,000 daltons. Studies carried out on the ability of the MMTV DNA polymerase to utilize a variety of natural and synthetic RNA and DNA template primers and to determine the requirements for DNA synthesis by this enzyme produced the following observations: (a) Mg+1 was the preferred divalent cation for DNA synthesis on all template-primers tested. (b) Poly (dC);Oligo (dG) was the most efficiently utilized synthetic template-primer. (c) Rates of DNA synthesis observed using activated DNA as a template were 20 to 25-fold those observed with 70S RNA as template. (d) Synthetic DNA-directed DNA synthesizing ability of the MMTV polymerase was found to be more sensitive to heat inactivation than other template-directed synthetic abilities. (e) Addition of inorganic phosphate at low concentrations to reaction mixtures was found to produce stimulation or inhibition of DNA synthesis, depending upon the template-primer directing that synthesis. (f) Apparent Km values for deoxynucleoside triphosphates were 10-15uM. (g) Purified preparations of MMTV DNA polymerase were found to be essentially free of DNase and RNase exonucleolytic activity except for RNase H activity.

31. EFFECT OF LONG-TERM INCUBATION ON RNA DEPENDENT DNA POLYMERASE (RDP) ACTIVITY IN MOUSE MAMMARY TUMOR VIRUS (MMTV).

Ashley RL, Manning JS
Dept. of Medical Pathology and Dept. of Bacteriology, Univ. of California, Davis, Ca 95616
Proc Am Assoc Cancer Res; 16:144 1975

The standard protocol for generating isotopically labelled DNA probes from MMTV templates involves prolonged incubation of the RDP reaction mixture. We find, however, that apparent production of cDNA ceases after the first three hours. Possible explanations for this profile included: (1) enzyme thermolability and (2) altered enzyme kinetics. These possibilities were tested in a series of preincubation experiments. Detergent-solubilized MMTV was preincubated at 37 degrees C for varying times in the presence or absence of cold nucleotides. Enzyme activity was then assayed by adding reaction mix with ^{3}H TTP with (exogenous) or without (endogenous) rAdT10. Appropriate controls and standards were incorporated into each experiment. 24 hr preincubation without nucleotides resulted in a 2X reduction in endogenous activity and a 7X reduction in exogenous activity, suggesting that MMTV RDP activity is temperature sensitive. 3 hr preincubation in the presence of nucleotides resulted in a 2X reduction of the endogenous activity; suggesting that a shift in equilibrium may occur favoring reannealing of the cDNA to the RNA template. These experiments indicate that factors such as enzyme thermolability and product reannealing may mean there is no quantitative advantage to prolonged incubation for generating probes. (Author Abstract)

32. ISOLATION AND CHARACTERIZATION OF RNA-DIRECTED DNA POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS (MEETING ABSTRACT).

Dion AS, Fout GS, Coriell LL, Moore DH
Inst. Med. Res., Camden, N.J.
Proc Am Assoc Cancer Res; 15:96 1974

RNA-directed DNA polymerase (RDDP) was isolated from purified milk-borne RIII virus (MuMTV) by DEAE- and phosphocellulose column chromatography. On phosphocellulose, RDDP activity was eluted with 0.4 M NaCl. The purified enzyme (z 100 fold) was found to have a molecular wt of 70-80,000 by SDS-polyacrylamide gel analysis, and utilized the following templates, in order of preference: poly rA;poly dT z poly rC;oligo dG z "activated" salmon sperm DNA z MuMTV 70 S RNA oligo dT z MuMTV 70S RNA. After purification on phosphocellulose, stored RDDP was found to be differentially labile, ie enzymatic DNA synthesis directed by poly rC;oligo dG was severalfold more labile than DNA-directed DNA synthesis.

33. ISOLATION AND CHARACTERIZATION OF RNA-DIRECTED DNA POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS.

Dion AS, Vaidya AB, Fout GS, Moore DH
Inst. Med. Res., Camden, N. J.
J Virol; 14(1):40-46 1974

RNA-directed DNA polymerase was isolated from milk-borne B-type murine mammary tumor virus (MuMTV) of the RIII mouse strain. The DNA polymerase sedimented as a single component with an estimated S20.w of 5.5S to 5.7S; the molecular wt was estimated at 98,000-102,000. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the phosphocellulose peak enzyme fraction demonstrated the enrichment of only one protein, which possessed a molecular wt of 100,000 and was presumably the polymerase enzyme. The purified enzyme was completely template dependent, responding most efficiently to poly(rC).oligo(dG); relatively less response was observed with "activated" salmon sperm DNA and MuMTV 70S RNA. Stability studies indicated differential lability dependent on the exogenous template used to monitor activity. The results did not support the existence of two viral DNA polymerases in RIII milk.

34. MOUSE MAMMARY TUMOUR VIRUS RNA-DEPENDENT DNA POLYMERASE: REQUIREMENTS AND PRODUCTS.

Dickson C
Imperial Cancer Res. Fund, London, England
J Gen Virol; 20(2):243-247 1973

Because mouse mammary tumor virus (MTV) differs from other members of the RNA tumor virus group with respect to its morphology and its antigenicity, an investigation was carried out to determine whether the requirements and

products of its RNA-dependent DNA polymerase might also differ. It was found that the enzyme required a divalent cation, all four deoxynucleotide triphosphates, dithiothreitol and a nonionic detergent to elicit activity. Further, the initial product appeared to be a rapidly sedimenting RNA:DNA hybrid, followed after longer incubation by a predominantly slow sedimenting DNA product. These results for the MTV polymerase were similar to those obtained with other RNA tumor viruses, despite the unique characteristics of MTV with respect to morphology and antigenicity.

35. CHARACTERIZATION AND SEPARATION OF VIRAL DNA POLYMERASE IN MOUSE MILK (MEETING ABSTRACT).

Howk RS, Rye LA, Killeen LA, Scolnick EM, Parks WP
Meloy Lab., Springfield, VA
Proc Natl Acad Sci USA; 70(7):2117-2121 1973

Previous demonstration of an RNA-directed DNA polymerase activity in mouse milk from a high mammary tumor virus (MTV) strain, RIII, provided a potential measure of viral activity in milk. Recent experiments of the authors showed that polymerase activity in mouse milk was partially and inconsistently inhibited by antisera against the type-C viral enzyme. Since one explanation of this variability was that the milk actually contained a mixture of type-B and type-C viral enzymes, they undertook in the present study to identify several viral enzymes in milk of RIII mice. Two were found, using fractionation on phosphocellulose and Sephadex G-100 columns. One was an RNA-directed DNA polymerase of type-C viruses; this enzyme which preferred manganese to magnesium in activity measurements using poly(rA) oligo(dT) as synthetic substrate was inhibited by specific sera, and had an apparent MW of 70,000. Milk from BALB/c and NIH Swiss mice contained a vast predominance of this C-type enzyme. The other DNA polymerase from RIII mouse milk which preferred magnesium to manganese was not inhibited by type C antipolymerase serum and appeared of larger molecular wt than the type-C polymerase. Its presence in milk from RIII mice and absence from milk of mice with low content of MTV correlates with the relative degree of type-B virus expression in these mice. Because of certain morphological similarities between murine MTV and the Mason-Pfizer monkey virus (MP-MV) isolated from a spontaneous breast tumor of a rhesus monkey, the authors also compared the MP-MV RNA-directed DNA polymerase with a gibbon type-C viral enzyme. The MTV and MP-MV polymerases both preferred magnesium as a divalent cation and eluted ahead of the type-C enzymes on chromatography, while the murine type-C enzyme and the gibbon enzyme were similar in cation preferences and in size. Thus, the MP-MV and gibbon type-C viral enzymes share similarities, resp, with the mouse type-B and mouse type-C viral enzymes. The apparent relationship between MTV and MP indicate the importance of obtaining evidence for additional similarities.

36. RNA-DEPENDENT DNA POLYMERASE IN PRENEOPLASTIC NODULES AND TUMORS OF THE MAMMARY GLAND OF BALB/C MICE.

Mukherjee AS, Banerjee MR
Tumor Biol. Lab., U. Nebraska, Lincoln, NB
J Natl Cancer Inst; 53(3):817-824 1974

Normal mammary tissue, preneoplastic nodules D1 and D8 of mouse mammary tumor virus (muMTV)-free BALB/c mice, an muMTV-positive D1 nodule, and the mammary neoplasms derived from each of these nodules were analyzed for RNA-dependent DNA polymerase (RDDP). In addition, 3-methylcholanthrene (MCA)-induced mammary tumors of BALB/c mice and muMTV-induced neoplasms of C3H mice were examined. The enzyme from the high-speed supernatant of tissue homogenate was purified by diethylaminoethyl-cellulose column chromatography by elution through a 0.05-0.7 M KCl gradient. RDDP was assayed in vitro at 37 C in a standard mixture containing Mg++ and kithiothreitol (DDT). The reaction was monitored by the rate of 3H-dTTP incorporation in an acid-insoluble fraction. Various synthetic polynucleotides and calf liver RNA were used as templates. RDDP was negligible in the mammary tissue of pregnant mice, modestly active in the D1 nodule, but highly active in the muMTV-free D8 and the muMTV-positive D1 nodules. In addition, it was extremely active in mammary neoplasms with or without muMTV, including the MCA-induced tumor. The enzyme from most tissues preferentially utilized poly rA.dT10 and calf liver RNA as templates. However, the D1-muMTV nodule enzyme had a poor affinity for the biologic RNA template and the enzyme from the MCA-induced tumor failed to use the same template. Prior treatment of the template with pancreatic and T1 (Aspergillus oryzae) RNAse abolished the activity, and the reaction was sensitive to dimethylbenzyldimethyl rifampicin. The reaction product was sensitive to DNAse but resistant to RNAse and NaOH. These results indicate the presence of and RDDP in muMTV-free mammary nodules and tumors. Between the two virus-free nodules, the RDDP activity was more pronounced in the lesion with a greater tumor potential.

37. DNA POLYMERASE ACTIVITY AND DNA SYNTHESIS IN PRENEOPLASTIC NODULE OUTGROWTH OF BALB/C AND C3H MOUSE MAMMARY GLAND.

Banerjee MR, Mehta RG, Wagner JE
Dept. Zool. Inst. Cellular Res., U. Nebraska, Lincoln
J Natl Cancer Inst; 50(2):339-345 1973

DNA polymerase activity and DNA synthesis in four outgrowth lines of preneoplastic nodules (HAN) of BALB/c and C3H mouse mammary gland were determined. The rate of 3H- thymidine triphosphate (3H-dTTP incorporation into trichloroacetic acid -insoluble material in vitro was used as a measure of DNA polymerase (DNA nucleotidyl transferase) activity in the postmicrosomal supernatant fraction of the HAN tissues. Incorporation of 3H-thymidine into DNA after a single intraperitoneal injection of the DNA precursor was used as a measure of DNA synthesis in the HAN cells in vivo. Both DNA polymerase and DNA synthesis in mammary tumor virus (MTV)-free and MTV-positive D1 nodule outgrowths of BALB/c mice were low. A relatively higher DNA polymerase activity and DNA synthesis were observed in the high tumor-producing, MTV-free D8 nodule of BALB/c mice. The highest level of DNA polymerase activity and DNA synthesis was in the high tumor-producing, MTV-positive CH33 nodule outgrowth line of C3H mice. Unlike the normal mouse mammary cells, both DNA polymerase activity and DNA synthesis in the preneoplastic lesions were independent of the ovarian hormones. The HAN outgrowth lines of both BALB/c and C3H mice, regardless of their tumorigenic potential, exhibit an altered responsiveness to normal regulation on DNA polymerase and DNA synthetic activities. The significance of this characteristic loss of normal control to suppress DNA polymerase and DNA synthesis in the preneoplastic lesions with regard to neoplastic transformation is discussed.

38. DETECTION OF RNA-INSTRUCTED DNA POLYMERASE AND HIGH MOLECULAR WEIGHT RNA IN MALIGNANT TISSUE (MEETING ABSTRACT).

Gulati SC, Axel R, Spiegelman S
Coll. Physicians Surgeons, Columbia U., New York, N. Y.
Proc Natl Acad Sci USA; 69(8):2020-2024 1972

An RNA-DNA hybridization technique has been used to detect 70S RNA-directed DNA synthesis in mouse mammary carcinomas. Breast tumors excised from tumor-bearing Paris RIII mice were homogenized and fractionated according to a procedure designed to eliminate cellular nucleases, polymerases and RNA. Glycero gradient centrifugation of the in vitro acid-insoluble tumor homogenate polymerase assay product showed a distinct virus-specific peak with a sedimentation coefficient of 70S, indicating the presence of viral RNA-directed DNA polymerase. No such activity was detected in homogenates of normal lactating breast tissue from tumor-free NIH Swiss mice. The ability to hybridize the 3H-labeled DNA product specifically to purified mouse mammary tumor virus (MMTV) RNA proved that the RNA-directed DNA polymerase was of MMTV origin. The 3H-DNA product of the MMTV polymerase could be used to detect virus specific RNA in polysomal fractions from mouse breast tumor homogenates. No virus-specific RNA was detected in polysomal fractions from livers of tumor-free NIH mice.

39. VIRION-ASSOCIATED AND CELLULAR RNA METHYLASE ACTIVITY IN NORMAL AND NEOPLASTIC MAMMARY TISSUE FROM MAMMARY TUMOR VIRUS-INFECTED AND -UNINFECTED MICE.

Gantt R, Smith GH, Julian BT
Building 37, Room 4D12, NIH, Bethesda, MD 20014
Cancer Res; 35(7):1847-1853 1975

The cell-free RNA methylase capacities and methylation patterns of prelactating, lactating, and neoplastic mammary tumors were comparatively studied. In addition, purified preparations of mouse mammary tumor virus (MMTV) and intracytoplasmic A particles were examined for the presence of RNA methyltransferase activity. Inbred mouse strains and sublines included BALB/c/He, BALB/cfC3H, BALB/c/CRGL, C3H /He, C3HfB/He, and C3H/StWi. Purified MMTV samples were obtained from infected milk, and the assay solutions of hydrolyzed RNA were subjected to column chromatography. When cell- free extracts were incubated with methyl-labeled S- adenosylmethionine (50 microCi) under limiting RNA conditions, differences in the extent of incorporation suggested qualitative differences in the methylase complements of the extracts. The extent of methylation did not correlate with the presence or absence of the standard MMTV(s) or low oncogenic strain MMTV(l) of MMTV. In studying two normal control tissues, the methylase activity of lactating tissue was twice that of 16 day pregnant tissue, suggesting functional changes and demonstrating the greater capacities of lactating tissue homogenates. A determination of the patterns of methylation in the four major nucleic acid bases indicated that the increased methylase activity of lactating tissue resulted from enhanced activity of all the methylases. Methylation patterns of MMTV(s) and MMTV(l) indicated that there were methylation differences, independent of the malignant state, resulting from the virus infection. RNA methylase assays in MMTV(s) virions revealed that activity is dependent on addition of both surfactant, for disruption of the virion envelope, and substrate RNA. The results suggest that the RNA methylases of mammary tumor tissue are qualitatively different from those of normal lactating mammary tissue, that no correlation exists between methylase capacity and either the malignant state or the etiological agent, and that qualitative effects are attributable to the presence of virus. These conclusions are consistent with the hypothesis that aberrant methylation of nucleic acids is a fundamental event in malignant conversion.

40. CATION PREFERENCES FOR POLY(RC).OLIGO(DG)-DIRECTED DNA SYNTHESIS BY RNA TUMOR VIRUSES AND HUMAN MILK PARTICULATES.

Dion AS, Vaidya AB, Fout GS
Inst. Med. Res., Camden, N. J.
Cancer Res; 34(12):3509-3515 1974

Assay of cation preferences of RNA tumor viruses for poly(rC).oligo(dG)-directed DNA synthesis showed that B-type murine mammary tumor virus and Mason-Pfizer monkey virus preferred magnesium. All mammalian C-type viruses preferred manganese. Ten of 25 (40%) human milk samples assayed contained DNA polymerase activity related to known mammary tumor-associated viruses, murine mammary tumor virus and Mason-Pfizer monkey virus, on the basis of (a) utilization of poly(rC).oligo(dG) as template primer for DNA synthesis, (b) buoyant density of particle-bound DNA polymerase activity in CsCl gradients, and (c) maximal poly(rC).oligo(dG)-directed DNA in the presence of Mg++, and lower activity in the presence of Mn++. Electron microscopy of phospholipase C-ether-treated particulate human milk fractions, possessing poly(rC).oligo(dG)-templated DNA synthetic activity, revealed the presence of numerous viral core-like structures. The latter also possessed relatively high levels of endogenous DNA polymerase activity by the simultaneous detection technique.

41. RNA-DEPENDENT DNA POLYMERASE ACTIVITY IN FIVE RNA VIRUSES: DIVALENT CATION REQUIREMENTS (MEETING ABSTRACT).

Scolnick E, Rands E, Aaronson SA, Todaro GJ
Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.
Proc Natl Acad Sci USA; 67(4):1789-1796 1970

This study compares the effects of manganese and magnesium on DNA synthesis by RNA-dependent DNA polymerase in Rauscher leukemia virus. Synthesis of DNA from viral RNA of intact virions occurred equally well with either magnesium acetate or manganese acetate. However, at limiting concentrations of divalent cation (1 x10**-3 M) manganese was more effective; with synthetic RNA polymer used as template, a 50- to 100-fold stimulation of activity occurred in the presence of manganese with optimal concentrations for synthesis from endogenous viral RNA being too high for optimal synthesis with the synthetic template. At either 4 x 10**-3 M magnesium or 4 x 10**-3 M manganese, DNA synthesis from endogenous viral RNA is optimal. Conditions that are optimal for detecting polymer-stimulated activity in murine leukemia virion are effective for murine mammary tumor virus and avian myeloblastosis virion. Two nononcogenic viruses, visna virus and primate syncytium-forming virus, exhibit similar DNA polymerase activity.

42. NO EVIDENCE FOR PARTICLES ENCAPSULATING RNA-INSTRUCTED DNA POLYMERASE AND HIGH MOLECULAR WEIGHT VIRUS-RELATED RNA IN HERPESVIRUS INDUCED TUMOURS OF NON-HUMAN PRIMATES.

Laufs R, Steinke H
Hygiene-Institut der Universitat D-34 Gottingen, Kreuzbergring 57 West Germany
J Gen Virol; 27(2):239-245 1975

Twelve tumorous spleens or lymph nodes from nonhuman primates with malignant lymphoma induced by oncogenic herpesvirus (Herpesvirus saimiri and H ateles) were

tested for the presence of particles encapsulating RNA - instructed DNA polymerase. These spleens and lymph nodes were negative for 3H-DNA-RNA complex in the 70S region of a glycerol sedimentation velocity gradient. This complex was present in mouse tumor induced with Rauscher leukemia virus (RLV) and mouse mammary tumor virus (MMTV). The presence of inhibition in the monkey tumor directed against DNA polymerase was excluded by reconstruction experiments using NC-37 cells infected with simian carcinoma virus type 1 (SSV-1). Only 3H-DNA was obtained from NC-37 cells infected with SSV-1 precipitated with ethanol and analyzed on Cs2SO4 gradients. Annealing experiments showed that 40% of the input 3H-DNA from SSV-1 hybridized to polysomal RNA from NC-37 cells infected with SSV-1 but no 3H-DNA hybridized to the polysomal RNA from herpesvirus-induced tumors. Attempts to demonstrate partial expression of the oncornavirus genome and determine an interspecies antigen related to monkey oncornaviruses were also negative. There was thus no evidence for the presence of RNA tumor virus in herpesvirus-induced malignant lymphoma of nonhuman primates.

43. SEROLOGICAL ANALYSIS OF REVERSE TRANSCRIPTASE OF THE MASON-PFIZER MONKEY VIRUS.

Yaniv A, Ohno T, Kacian D, Colcher D, Witkin S, Schlom J, Spiegelman S
Columbia U. Coll. Physicians Surgeons, New York, N. Y.
Virology; 59(1):335-338 1974

Antiserum prepared against the partially purified DNA polymerase of Mason-Pfizer monkey virus (MPMV) neutralized the endogenous DNA polymerase of that virus and of X381 virus, an agent which is morphologically indistinguishable from MPMV and which was isolated from cultures prepared from the lactating mammary gland of a rhesus monkey. Anti-MPMV DNA polymerase did not inhibit the DNA polymerase activity of avian myeloblastosis virus, Rauscher and Friend murine leukemia viruses, feline leukemia virus, murine mammary tumor virus, or simian sarcoma virus.

44. REVERSE TRANSCRIPTASE OF RNA TUMOR VIRUSES: IMMUNOLOGICAL RELATIONSHIPS.

Todaro GJ, Aaronson SA, Scolnick EM, Ross J, Parks WP
Natl. Cancer Inst., Bethesda, MD
Bibl Haematol; 39):269-271 1973

Studies were undertaken to determine if RNA-dependent DNA polymerase (reverse transcriptase) was specifically restricted to certain RNA tumor viruses and whether it was specifically restricted to tumor cells. All the oncogenic RNA viruses tested so far have DNA polymerase, as indicated both by the endogenous reaction with the viral RNA and by synthetic polymer-stimulated reactions with such templates as poly rA.rU, poly rI.rC and poly rA.dT. With the exceptions of visna and 'foamy' viruses, nononcogenic RNA viruses have shown non evidence of DNA polymerase activity. The polymerase seems to be a viral specific enzyme which is not found in normal cells. Despite the diversity of species of origin, host range, and biological properties of viruses with reverse transcriptase, the enzyme is uniform in its template characteristics and can be distinguished from cellular DNA polymerase. Murine virus leukemia polymerase has been partially purified and used to produce an antibody in rabbits. The antibody also inhibits the enzymatic activity of hamster, rat, and cat leukemia polymerase, it does not inhibit mouse mammary tumor virus and avian leukemia virus polymerase. An antibody prepared against the avian virus (Rous sarcoma virus) polymerase inhibits the polymerase of all major avian C-type viruses, but not any mammalian C-type virus polymerases. Thus, antibody to the reverse transcriptase will be useful not only in distinguishing C-type viruses from other retraviruses but also in identifying the species of origin of a particulate C-type virus isolate.

45. PROPERTIES OF ADENYLATE CYCLASE OF MURINE MAMMARY CARCINOMA.

Schorr I, Russell A
Hadassah Univ. Hosp., Jerusalem, Israel
Biochim Biophys Acta; 364(2):173-180 1974

The activity of adenylate cyclase was studied in mammary carcinoma tissue and normal lactating tissue from BALB/c mice infected through suckling by C3H mammary tumor virus-carrying mice. The enzyme activity was identified primarily within the 1000 x g fraction of the whole homogenate of the carcinoma tissue; it was not identified in the same fraction of the whole homogenate of the normal lactating tissue. In the cancer tissue, the optimal ATP concentration for maximal enzyme activity appeared to be 1 mM. The optimal incubation period for the enzymatic reaction was five minutes, and the optimal Mg2+ concentration for maximal adenylate cyclase activity was 6mM. However, in the presence of 10 mM NaF, peak activity was observed at 8 mM Mg2+. Enzymatic activity peaked at pH 8.2 and was proportional to the protein concentrations between 0.23 and 1.86 mg/ml. Of a variety of hormones tested, only epinephrine consistently stimulated the enzymatic activity; this stimulation was completely inhibited by propranolol and almost unaffected by phentolamine. Essentially no enzyme activity was found in the 105,000 x g fraction of the carcinoma tissue. It is at present difficult to ascribe physiological significance to the prostaglandin effect on tumor cyclase.

46. MICROSOMAL N-ACETYL-GLUCOSAMINYL-TRANSFERASES ACTIVITY IN BALB/C MICE INFECTED WITH MOUSE MAMMARY TUMOR VIRUS (M-MTV).

Gorka C
Departement de Recherche Fondamentale, Laboratoire de Biologie Cellulaire, Centre d'Etudes Nucleaires de Grenoble, 85 X, F-38041 Grenoble Cedex (France)
Experientia; 33(5):659-660 1977

N-acetyl-glucosaminyl transferase in spleen cells of mice infected with M-MTV is enhanced. This increased synthesis of glycoprotein is not due to synthesis of new enzyme. Such a result suggests that the spleen is implicated in the infecting process. (13 Refs) (Author Abstract)

C. Biochemical Studies of MuMTV Structural Components

47. CHARACTERISTICS OF THE STRUCTURAL COMPONENTS OF THE MOUSE MAMMARY TUMOR VIRUS: I. MORPHOLOGICAL AND BIOCHEMICAL STUDIES.

Sarkar NH, Nowinski RC, Moore SH
Sloan-Kettering Inst., New York, N.Y.
Virology; 46(1):1-20 1971

The isolation of the subviral components of the mouse mammary tumor virus (MTV) is described. Milk from inbred mice of strains susceptible to mammary tumors was used as a source of virus. The virus was purified by the use of different density gradient centrifugation and, after treatment with Tween 80-ether, the aqueous extract was further purified and fraction I, containing viral nucleoids, some damaged virions, and disrupted membranes, was separated from fraction II. Isolated viral nucleoids and purified MTV were treated with pancreatic ribonuclease. The buoyant density of the nucleoid in potassium citrate or tartrate is 1.24 g/cm3 as compared to

1.16-1.18 g/cm3 for the untreated virus. In negatively stained preparations the MTV nucleoids are pleomorphic with most forms being spherical. The viral nucleoid contains 4.4% RNA and the intact virus shows 1.9% RNA. Nucleoid capsules are resistant to protease and can be isolated by density-gradient centrifugation; they have the morphological appearance of empty bags, and probably contain either lipid or carbohydrate, since their density is 1.14 g/cm3. The high degree of order of spikes and the regular structure of the membrane suggest that the viral membrane has a characteristic symmetry that is distorted in preparation for electron microscopy.

48. CHARACTERISTICS OF THE STRUCTURAL COMPONENTS OF THE MOUSE MAMMARY TUMOR VIRUS: II. VIRAL PROTEINS AND ANTIGENS.

Nowinski RC, Sarkar NH, Old LJ, Moore DH, Scheer DI, Hilgers J
Sloan-Kettering Inst., New York, NY
Virology; 46(1):21-38 1971

An immunological analysis of the mouse mammary tumor virus (MTV) structural proteins is reported; several separate but related series of experiments were involved. MTV was purified from the milk of congenitally MTV-infected C3H/An and C3H/HeJ mice and treated with Tween 80 ether to bring about the release of subviral components. Soluble virus proteins were chromatographed on Sephadex G-200 and used as antisera to immunize rats; five serologically distinct viral antigens were identified by these antisera (MTV-s1, s2, s3, s4 and s5). Antigens s1 and s2 were group-specific, and were the antigens of the viral nucleoid. The MTV-s3 antigen was a structural protein of the viral membrane. Antisera prepared against MTV or isolated MTV proteins did not react with murine leukemia virus antigens; nor did antisera against the latter virus react with MTV antigens. Polyacrylamide gel electrophoresis of SDS-disrupted MTV showed five major proteins of the virion (p1-p5); molecular weights of these five proteins were estimated as; p1, 90,000; p2, 70,000; p3, 52,000: p4, 33,000; and p5, 23,000. The p3 protein was the major protein of the virus; p3 was found in the nucleoid and carried the s1 antigen. Antisera against MTV proteins were used in immunofluorescence tests to determine the intracellular deposition of viral structural components. All immunofluorescence reactions with MTV antisera were cytoplasmic; no nuclear fluorescence was seen. Rabbit anti-MTV serum was used in immunodiffusion tests to detect MTV antigens in extracts of a wide variety of neoplastic tissues. Results indicated that MTV infection was restricted to three neoplastic tissues: mammary tumors of MTV-infected mice; ML+ leukemias; and Leydig cell tumor of MTV-infected mice. Rat antisera against isolated MTV proteins were used in immunodiffusion tests to identify individual viral components in virus-infected cells. All extracts of mammary tumors and ML+ leukemias were positive for the s1 and s2 antigens. Electron microscopic examination of three ML+ leukemias and the Leydig cell tumor revealed large intracytoplasmic inclusions of A-type particles, but revealed no budding virions.

49. VARIATIONS IN THE SURFACE OF MUMTV FROM DIFFERENT SOURCES (MEETING ABSTRACT).

Sheffield JB, Daly TM, Taraschi N
Institute for Medical Research, Camden, New Jersey, 08103
Proc Am Assoc Cancer Res; 17:140 1976

The constituents of the surface of MuMTV derived from the milk of 2 mouse strains (RIII and BALB/cfC3H) have been compared with those of virus obtained in vitro from a continuous tumor cell line (BALB/cfC3H). Iodination with lactoperoxidase indicated that the major external proteins of milk virus were gp68 and gp55, while gp55 was the only external protein of in vitro virus. The major external polysaccharide in the milk virus, determined by galactose oxidase-borotritide (GOB) labeling was associated with gp140, whereas gp55 and gp36 were associated with the major external polysaccharides of virus produced in vitro. The surface of the virions appeared similar by negative-stain e.m but freeze-etch studies indicated that the pitted surface coat of the milk virus was missing from the in vitro virus. It thus appears that there are variations in the surface of MuMTV which are a function of the source of virus. (Author Abstract)

50. EXTRINSIC LABELING OF MUMTV WITH A GALACTOSE OXIDASE-TRITIATED BOROHYDRIDE METHOD.

Sheffield JB, Daly TM
Inst. for Medical Res., Copewood St., Camden, NJ 08103
Virology; 70(1):247-250 1976

As part of a study of the detailed structure of the surface of the mouse mammary tumor virus (MuMTV), accessible glycoproteins (gp) were labeled by reduction with KB^3 H4 after enzymatic oxidation of galactose residues. Sodium dodecyl sulphate-polyacrylamide gel electrophoresis showed that oxidation and reduction occurred principally in gp140, gp90, and gp36, as well as in large molecules that did not enter the gel, and in a low molecular weight material. A small amount of gp50-60 was also labeled. The results suggest that the surface of MuMTV is highly complex.

51. MICROFILAMENT POLYMERIZATION AND VIRUS PRODUCTION (MEETING ABSTRACT).

Damsky CH, Sheffield JB, Warren L
Wistar Inst., Philadelphia, PA 19104
J Cell Biol; 70(2/Part2):117a 1976

We have reported a protein associated with murine mammary tumor virus (MuMTV) which comigrates with muscle actin on both SDS and urea gels. An actin-like protein has also been reportedly associated with many other enveloped viruses. ^{125}I labeling of intact and disrupted MuMTV preparations has shown that the actin is within the particle and not absorbed from the medium (milk) during isolation (I). We have now eliminated the possibility that the actin is due to the presence of virus free vesicles which are sloughed off from the actin-rich cell surface during lactation and which co-purify with the virus. Milk from virus free and virus infected animals was subjected to the purification procedure used for MuMTV and the vesicle population from virus free milk was compared with the standard preparation. Quantitative analysis of SDS gels reveals that the actin content of both preparations is very similar. Examinations of negatively stained and sectioned preparations of virus reveals only 10-15% contamination by virus free vesicles. Therefore most of the actin associated with the virus preparations must be a true component of the virus particles. MuMTV is pinched off from the ends of long microfilaments containing microvilli. The distal ends of some microfilaments appear embedded in the virus core. We have now observed in grazing thin sections that the filaments show attachment by cross bridges to the membrane along the entire length of the microvillus. We suggest that 1) MuMTV is extruded as a consequence of microfilament polymerization and microvillus growth and 2) some microfilament actin is retained by the virus when it is pinched off and is the source of the actin associated with the interior of the mature virus particle. The ultrastructural data also raise the possibility that virus nucleoids can act as nucleation sites for microfilament polymerization.

52. ACTIN IN MAMMARY TUMOR VIRUS (MEETING ABSTRACT).

Damsky CH, Tuszynski GP, Sheffield JB, Warren L
Wistar Inst., 36th and Spruce Sts., Philadelphia, Pa.
Biophys J; 16(21-part2):116a 1976

A protein comigrating with purified chick muscle actin was observed when gradient purified murine mammary tumor virus (MuMTV) was separated using sodium dodecyl sulfate (SDS) discontinuous polyacrylamide gel electrophoresis. The protein comprised 1-2% of the virus protein. To demonstrate that this protein is an actin, the protein was eluted from a stained and fixed SDS preparative slab gel of MuMTV; the SDS was then removed from the protein by electrodialysis in the presence of 8M urea and the SDS-free protein was run on an acid-urea continuous polyacrylamide gel system in a sample buffer containing 5% triton, 5% acetic acid, 5% mercaptoethanol pH 2.5. The putative virus actin comigrated with both chick muscle actin which had undergone the same processing procedure, and chick muscle actin which had not been run on an SDS gel. Since there is a major protein component in both virus-free mouse milk and tissue culture fluid which comigrates with actin, it was essential to rule out the nonspecific binding of an actin-like protein to the outside of the virus during isolation. Labeling studies on intact and disrupted virus using ^{125}I indicated that most or all of the actin is located inside the virus particle. MuMTV particles are released into the lumen of the mammary gland from the ends of long microvilli. Bundles of microfilaments are visible within these microvilli and can be seen to impinge on the virus particles at the ends of the microvilli. Whether actin plays a role in transport of incomplete particles to the cell membrane, virus release or virus infectivity is unknown.

53. IDENTIFICATION OF THE MAMMARY TUMOR VIRUS ENVELOPE GLYCOPROTEIN (GP52) ON MOUSE MAMMARY EPITHELIAL CELL SURFACE.

Yang J, Tang R, Nandi S
Cancer Res Lab., Univ. California, Berkeley, CA 94720
Biochem Biophys Res Commun; 76(4):1044-1050 1977

The mammary tumor virus (MTV) envelope glycoprotein (gp 52) on the cell surface of tumor (BALB/cfC3H) and normal (BALB/cfC3H and BALB/c) mammary epithelial cells was examined in monolayer culture utilizing the lactoperoxidase radioiodination method. Radioiodination of cells followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis analysis revealed only a few distinct peaks. The presence of gp 52 on the cell surface was affected by both cell density and hormones. GP 52 was not found on the surface of normal mammary epithelial cells from virus-free BALB/c mice but was noted on the surface of cells from chronically infected BALB/cfC3H mice. Cells cultured in the presence of hydrocortisone consistently revealed radioiodinatable gp 52, whereas those cultured in the absence of hormone showed either undetectable or very reduced amounts. Cells cultured at a higher density revealed more radioiodinatable gp 52 on their surfaces compared with the same cells seeded at a lower density. There may be a correlation between abundance of radioiodinatable gp 52 on the cell surface and production of MTV into the culture medium. (20 Refs)

54. GLYCOPEPTIDE PATTERNS OF MOUSE MAMMARY GLANDS AND TUMORS. (MEETING ABSTRACT).

Sheffield JB, Buck CA, Warren L
Inst for Medical Res, Camden, N. J. 08103,
Proc Am Assoc Cancer Res; 18:189 1977

It has been shown that glycopeptides released from transformed fibroblasts by pronase treatment of cell trypsinates are larger than those released from control cells, and appear as an identifiable peak (peak A) after passage through a Sephadex G-50 column. This observation has recently been extended to melanomas and hepatomas maintained as solid tumors. We are concerned with the appearance of these glycopeptides in a tumor arising within an animal, and have chosen to examine mammary tumors induced in the mouse by MuMTV. C57fRIII mice bearing a tumor, and C57 control mice were labeled with either ^{14}C or ^{3}H glucosamine, the tissues were excised and the glycopeptides prepared by pronase digestion of suitable fractions and passed through a column of Sephadex G-50. The digest from the tumor contained a prominent peak A which was lacking from the digests of resting mammary gland fractions. However, peak A was found in extracts of mid-pregnant and lactating control mammary gland. In earlier studies, the glycopeptide elution pattern from normal cells was only slightly affected by their growth or functional status. In the mammary gland, however, growth and function do appear to play a major modulating role with respect to glycopeptide structure. (Author Abstract)

55. STRUCTURAL COMPONENTS OF MOUSE MAMMARY TUMOR VIRUS. I. POLYPEPTIDES OF THE VIRION.

Yagi MJ, Compans RW
Dept. Microbiology, Univ. Alabama Medical Center, Birmingham, AL 35294
Virology; 76(2):751-766 1977

Twelve polypeptides associated with mouse mammary tumor virions (mMTV), 4 major polypeptides and 6-8 minor proteins were analyzed. Three of the major proteins, with estimated molecular wts of 37,000, 52,000, and 60,000, are glycoproteins (gp). Labeling with ^{35}S-sulfate revealed significant amounts of sulfate covalently linked with gp60 and gp52. Variations in the polypeptide pattern of mMTV were observed when virions were grown and labeled under different culture conditions. The virions were morphologically unaltered after incubation with protease; however, both gp60 and gp52 were absent from the polypeptide patterns. These results indicate that cleavage of gp60 and gp52 is not unlikely during ingestion and digestion of mothers' milk by neonatal mice, and therefore, even if cleavage is not necessary for infectivity of the particle, it may not interfere with infectivity in vivo. (32 Refs)

56. PRECURSOR-PRODUCT RELATIONSHIP BETWEEN NONGLYCOSYLATED POLYPEPTIDES OF A AND B PARTICLES OF MOUSE MAMMARY TUMOR VIRUS.

Tanaka H
Inst. Virus Res., Kyoto Univ., Kyoto, Japan
Virology; 76(2):835-850 1977

In a comparative study of various intracytoplasmic particles of mouse mammary tumor virus, sodium dodecyl sulfate-polyacrylamide gel electrophoresis revealed that B particles consisted of three major nonglycosylated polypeptides of varying molecular wt and six glycopeptides. All A-particle polypeptides were nonglycosylated. The polypeptide composition of A particles was different from that of B particles. The only common major component was band p7 and three other bands of variable amounts, p43, p37, and p13. After incubation at 37 C for 20 hr, A particles showed a change of pattern; major bands disappeared except for A-p43, A-p37 and A-p7, and a strong new band, A-p25, appeared. No ultrastructural alteration was observed. This conversion was inhibited by diisopropylfluorophosphonate. When purified in the presence of phenylmethanesulfonyl fluoride, A particles consisted of a single major polypeptide, A-p70. Incubation of these A particles resulted in generation of A-p15 in addition to A-p25 and A-p7 at the sacrifice of A-p70. These studies plus

studies of antigens indicate that the three major internal components of B particles are generated from a common precursor, A-p70, through enzymatic cleavage and, hence, that A particles are the real pronucleocapsids of B particles. (55 Refs)

57. POLYPEPTIDES OF THE MOUSE MAMMARY TUMOR VIRUS. I. CHARACTERIZATION OF TWO GROUP-SPECIFIC ANTIGENS.

Sarkar NH, Dion AS
Inst. Med. Res., Camden, N.J.
Virology; 64(2):471-491 1975

The polypeptide composition of the mouse mammary tumor virus (MuMTV) was analyzed by polyacrylamide-gel electrophoresis in the presence of sodium dodecyl sulfate (SDS-PAGE). Antigen p55 was the most prominent viral protein and was common to viruses isolated from RIII, C3H, GR, and A mice. Polypeptide 28 was not a glycoprotein and antisera against purified p28 did not react the viral surface. Immunodiffusion assays indicated that p55 and p28 were immunologically unique and that p28 shared a common antigen determinant with the intracytoplasmic A particles, probably with Ap29. P28 was a common antigen in the RIII, C3H, GR, and A viruses. The data indicate that p55 is a component of the viral surface and that it is a group-specific antigen (gs-1) of MuMTV. In contrast, p28 is most likely a major group-specific internal antigen (gs-2) of MuMTV. Purified intracytoplasmic A particles from spontaneous lymphoid leukemias of DBA/2 mice were also analyzed. SDS-PAGE of MuMTV reproducibly resolved at least 11 polypeptides, the molecular weights of the major polypeptides being 55,000 (p55), 34,000 (p34), 28,000 (p28), 18,000 (p18), and 12,000 (p12). P55 and p34 were characterized as glycoproteins on the basis of staining with periodic acid-Schiff reagent and the incorporation of labeled glucosamine. The intracytoplasmic A particles contained five polypeptides of molecular weight 52,000 (Ap52), 43,000 (Ap43), 37,000 (Ap37), 29,000 (Ap29), and 15,000 (Ap15). Antisera against p55 were able to precipitate intact virus.

58. POLYPEPTIDES OF THE MOUSE MAMMARY TUMOR VIRUS. II. IDENTIFICATION OF TWO MAJOR GLYCOPROTEINS WITH THE VIRAL STRUCTURE.

Sarkar NH, Taraschi NE, Pomenti AA, Dion AS
Memorial Sloan-Kettering Cancer Center, New York, NY 10021
Virology; 69(2):677-690 1976

In order to localize the major structural polypeptides of the murine mammary tumor virus (MuMTV), three subviral fractions were prepared, examined by electron microscopy, and analyzed by polyacrylamide gel electrophoresis (PAGE) in the presence of sodium dodecyl sulfate. Treatment of intact virus with 0.05 N HCl at 4 C for 20 min resulted in the removal of the characteristic surface projections of the virus. Viral membrane fragments with attached projections (rosettes), consisting of stalks and knobs, were prepared by treating MuMTV with Tween-80 and ether. The buoyant density (in sucrose gradients) of the particles after removal of the projections was 1.181 g/cm^3, as compared with 1.171 g/cm^3 for the intact virus. PAGE analysis of the viral material released by the action of acid (for 20 min at 4 C) revealed two glycoproteins of 55,000 (gp55) and 68,000 (gp68) molecular weight (MW), gp55 being the major species. The polypeptide composition of the projectionless particles was complex; the major component was a glycoprotein of 34,000 MW (gp34). Although intact virus contained only one glycoprotein (gp55) in the 50,000-60,000-MW range, the projectionless particles were found to contain two minor components within the same MW range, only one of which was a glycoprotein. The nonglycopeptide component with an apparent MW of 51,000 (p51) appeared to be a normal minor protein constituent of MuMTV. The viral rosettes were found to contain gp34, gp55, gp68, and an additional glycoprotein of MW 90,000 (gp90). A comparison of the morphology and polypeptide composition of the intact virus and subviral components suggests that the knobs of the viral projections are composed of gp55. The gp34 component is associated with the viral membrane and may be situated within the membrane bilayer from which the projections protrude.

59. IDENTIFICATION OF A PRECURSOR PROTEIN TO THE MAJOR GLYCOPROTEINS OF MOUSE MAMMARY TUMOR VIRUS.

Dickson C, Puma JP, Nandi S
Cancer Research Laboratory, University of California, Berkeley, California 94720
J Virol; 17(1):275-282 1976

Mouse mammary tumor virus-producing cultures of mouse mammary tumor cells synthesize a viral-related polypeptide of molecular weight of 73,000 (gp 73) which is rapidly labeled during a short pulse but disappears during the chase concomitantly with the appearance of label in the virion glycoproteins gp 49 and gp 37.5/33.5. The addition of the protein synthesis-inhibitor cycloheximide to the chase medium has little effect on this conversion. Treatment of the proposed precursor with .alpha-chymotrypsin leads to the formation of a polypeptide of molecular weight 49,000, similar to the major virion glycoprotein. A comparison of tryptic digest maps of the glycoproteins involved supports the hypothesis that both the viral glycoproteins gp 49 and gp 37.5/33.5 are derived from gp 73.

60. EXPRESSION OF MOUSE MAMMARY TUMOR VIRAL POLYPEPTIDES IN MILKS AND TISSUES.

Noon MC, Wolford RG, Parks WP
Natl. Cancer Inst., Bethesda, Md.
J Immunol; 115(3):653-658 1975

A 14,000-dalton polypeptide (p14) from RIIi murine mammary tumor virus (MMTV) was isolated by column chromatography in 6 M GuHCl. Antiserum prepared in rabbits specifically precipitated 125I -labeled p14; in double antibody competion, radioimmunoassays performed with limiting amounts of antibody, both purified p14 and disrupted MMTV, competed specifically with labeled antigen. The expression of this MMTV type B virus antigen could be measured by competition radioimmunoassays in milks, mammary glands, tumors, and tissue culture cells. MMTV expression measured by p14 immunoassay correlated well with the spontaneous incidence of mammary adenocarcinomas in different murine strains but not with type C MuLV p30 antigen expression. Levels of MMTV gp52, the major type-B viral glycoprotein, corresponded to p14 levels, suggesting that their control is comparably regulated. Evidence that this molecular weight polypeptide is present in feral and inbred strains of widely differing geographic origin and in MMTV with apparently different biologic properties suggests surprising conservation of MMTV protein homology.

61. STRUCTURE OF THE MOUSE MAMMARY TUMOR VIRUS: POLYPEPTIDES AND GLYCOPROTEINS.

Teramoto YA, Puentes MJ, Young LJ, Cardiff RD
Sch. Med., U. California, Davis
J Virol; 13(2):411-418 1974

The polypeptide and glycoprotein composition of mouse mammary tumor virus (MTV) virions obtained from primary monolayer cultures of BALB/cfC3H mouse mammary tumor cells was studied by polyacrylamide gel electrophoresis using internal and external labeling and Coomassie blue and periodic acid Schiff (PAS) staining. Twelve polypeptides were reproducibly resolved using the combined methods. Five

major polypeptides with estimated molecular weights of 52,000, 36,000, 28,000, 14,000, and 10,000 daltons were demonstrated. Seven minor polypeptides with estimated molecular weights of 70,000, 60,000, 46,000, 38,000, 30,000, 22,000, and 17,000 daltons were also consistently detected. Carbohydrate was associated with five of these polypeptides as measured by PAS staining and/or (3H)glucosamine labeling; these glycoproteins had estimated molecular weights of 70,000, 60,000, 52,000, 36,000, and 10,000 daltons. The majority of the PAS stain and glucosamine was incorporated into the 52,000 and 36,000 dalton peaks.

62. STUDY OF THE COMPOSITION OF LIPIDS AND PROTEINS IN TWO STRUCTURES ISOLATED FROM THE MILK OF INFECTED MICE: MAMMARY TUMOR VIRUS AND THE MEMBRANE OF MILK GLOBULES.

Calberg-Bacq CM, Francois C, Gosselin L, Osterrieth PM, Rentier-Delrue F
Laboratorie de Microbiologie generale et medicale, Universite de Liege, Liege, Belgium
Arch Int Physiol Biochim; 83(5):948-949 1975

The biochemical study of the envelope of the mammary tumor virus and of the membrane of fatty milk globules (FMG) of a mouse showed that phosphatidylethanolamine was the major component of both. Both had high levels of phosphatidylserine and sphingomyelin as well as elevated choline and noncholine ratios. The virus, however, had three times as many lipids and a higher cholesterol:phospholipid ratio than the FMG. The virus also had seven glycopolypeptides as opposed to four in FMG. If, as hypothesized, these two structures are connected with the plasma membrane of the secretory cells, then the differences between them suggest that their secretion through budding would be consecutive to a membranous reorganization into structurally specific localized units.

63. EFFECT OF TRYPSIN ON MOUSE MAMMARY TUMOR VIRUS.

Sheffield JB, Zacharchuk CM, Taraschi N, Daly TM
Institute for Medical Research, Camden, New Jersey 08103
J Virol; 19(1):255-266 1976

Undisrupted mouse mammary tumor virus (MuMTV) derived from the milk of RIII mice has been analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and electron microscopy after treatment with insolubilized trypsin. No alterations were found in viral fine structure by either freeze-etch or negative-stain electron microscopy. No alterations were found in the ability of trypsinized virus to compete in a radioimmune assay for viral antigens. Infectivity experiments indicate no significant differences in the ability of treated virus to infect C57Bl mice. However, significant differences were observed in polypeptide composition. The intensely periodic acid-Schiff-positive band, gp140, was shown by galactose oxidase-borotritide labeling to be degraded into a fragment of 125,000 molecular weight. The major glycoprotein, gp55, was split into fragments of 36,000 and 23,000 molecular weight, both of which stained with periodic acid-Schiff stain. Gp68 was removed from the virus. Experiments with purified, iodinated gp55 showed that the trypsin-induced fragments of gp55 were immunologically active. We conclude that: (i) certain glycoproteins at the surface of MuMTV are accessible to an insoluble form of trypsin; (ii) the trypsin causes a nick in the polypeptide chain without affecting the configuration of the molecule; (iii) the nicked molecules remain bound to the virus; and (iv) the presence of these nicked molecules does not interfere with the biological or antigenic expression of virus function. (Author Abstract)

64. EFFECT OF HUMAN MILK ON THE MOUSE MAMMARY TUMOR VIRUS.

Sarkar NH, Charney J, Dion AS, Moore DH
Inst. Med. Res., Camden, N. J.
Cancer Res; 33(3):626-629 1973

The extent of mouse mammary tumor virus (MuMTV) virion degradation, the loss of infectivity, and the reduction in RNA-dependent DNA polymerase caused by some human milks was examined. MuMTV when mixed with whole, skimmed, or cream fractions of some human milks and incubated at 37 C for 18 hr resulted in degradation of the particle morphology and decreased infectivity and reverse transcriptase activity of the virions. The cream fraction was more effective in the physical, biochemical, and biological degradation of the virions than the whole or skimmed milk, but the nature of the degrading component(s) has not been determined. It segregates with the fat fraction of the human milk; either a chemical, enzymatic, or physical mechanism is possible. It appears that the primary effect upon the virus is to render the virion permeable. This may suffice to degrade the virion structure and in turn reduce infectivity. The presence of these degrading components in human milk may account for the difficulty of detection of the putative human mammary tumor agent.

65. DETECTION OF THE MAJOR GLYCOPROTEINS OF FRIEND LEUKEMIA VIRUS (GP71) AND THE MURINE MAMMARY TUMOR VIRUS (GP52) ON THE SURFACE OF MOUSE CELLS.

Holder WD, Peer GW, Bolognesi DP, Wells SA
Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710
Cancer Res; 36(6):3217-3224 1976

Specific rabbit antisera to the major glycoproteins of Friend leukemia virus (gp71) and the mouse mammary tumor virus (gp52) were utilized to study the surfaces of C3H-, DBA-, BALB/c-, and C57BL-transformed and normal cells by immunoelectron microscopy. Antiserum to gp71 showed reactivity with all of the mouse cells tested regardless of strain, virus production, or state of transformation. In cells producing murine leukemia virus, budding viruses and other areas of the cell surface were consistently labeled with gp71 antiserum. A gp52-like antigen was likewise detected on both cell surfaces and virions of C3H and DBA cells producing the mammary tumor virus. Budding virions with surface spikes but with crescent-shaped nucleoids in C3H/HeJ cells were labeled specifically with gp52 antiserum. The antigen localized with anti-gp52 serum was detected in low concentration on the surface of nonvirus-producing cultures of a C57BL/6 sarcoma induced by the Schmidt-Ruppin D strain of Rous avian sarcoma virus (SRD-2), a BALB/c bone marrow culture (JLS-V9), and a normal BALB/c fibroblast culture (BALB/cF). Other cell cultures transformed by either C-type virus or methylcholanthrene failed to demonstrate gp52 antigen. Both gp52- and gp71-like antigens were found to be expressed simultaneously in C3H/HeJ, C3H-MT, DBA-MT, SRD-2 (transformed) and BALB/cF, JLS-V9, and C3H-1 (normal) cultures. Expression of gp52 antigen in the absence of gp71 was not detected in any of the cultures examined. These findings demonstrate the ubiquitous expression of gp71 in a wide variety of normal and transformed mouse cells while gp52 tends to be expressed predominantly in cells from mice with high mammary tumor incidence (C3H and DBA), but only to a minor extent in cells from low mammary tumor incidence strains (BALB/c and C57BL). (Author Abstract)

66. SIALYLATION OF GLYCOPROTEINS OF MURINE MAMMARY TUMOR VIRUS, MURINE LEUKEMIA VIRUS, AND MASON-PFIZER MONKEY VIRUS.

Schloemer RH, Schlom J, Schochetman G, Kimball P, Wagner RR
Dept. Microbiology, Indiana Univ. Sch. Medicine, Indianapolis, IN 46202
J Virol; 18(2):804-808 1976

Neuraminidase treatment of mouse mammary tumor virus, Rauscher murine leukemia virus, and Mason-Pfizer monkey virus resulted in loss of their capacity to inhibit hemagglutination of influenza virus. Hemagglutination-inhibition activity of these RNA viruses could be restored by in vitro resialylation catalyzed by sialyl transferase. The major glycoprotein in the intact envelope of desialylated and, to some extent, native virions could be specifically labeled in vitro with cytosine monophosphate**-14 C-sialic acid. These studies further characterize the individual glycoproteins of mouse mammary tumor virus, Rauscher murine leukemia virus, and Mason-Pfizer monkey virus. (25 refs)

67. STRUCTURAL CHARACTERISTICS OF SOME MURINE RNA TUMOR VIRUSES STUDIED BY LACTOPEROXIDASE IODINATION (MEETING ABSTRACT).

Witte ON, Weissman IL, Kaplan HS
Stanford U. Sch. Med., Calif.
Proc Natl Acad Sci USA; 70(1):36-40 1973

Radiation leukemia virus (RadLV), Moloney leukemia virus (MLV) and mouse mammary tumor virus (MTV) were purified on discontinuous sucrose gradients and subjected to lactoperoxidase iodination. Protein constituents of the viruses were examined in Coomassie blue-stained 7% acrylamide gel electrophoresis studies. RadLV and MLV showed distinctive and similar protein spectra; each had six different major protein bands in which the Coomassie blue-positive material was found mostly in the four lower molecular wt proteins (10,000-30,000). MTV showed five protein bands. Lactoperoxidase iodination labeled one major protein in each virus: an 80,000 dalton protein in RadLV and MLV, and 52,000 dalton protein in MTV. These were thought to be enzyme-accessible surface proteins, while the lower molecular wt protein bands were thought to be enzyme-inaccessible proteins.

II. GENERAL STUDIES ON THE DETECTION AND CHARACTERIZATION OF MuMTV

68. IDENTIFICATION OF THE VIRIONS IN THE IN VITRO L1210(V) LEUKEMIA CELL LINES BY MORPHOLOGICAL, VIROLOGICAL, AND IMMUNOLOGICAL TECHNIQUES.

Chen PL, Hutchison DJ, Sarkar NH, Kramarsky B, Moore DH
Inst. Med. Res., Camden, N. J.
Cancer Res; 35(3):718-728 1975

Studies of the structural and biological features of virus in two cell lines, L1210(V) Glu- and L1210(V) Asn-, are reported. Sera used in immunological tests included: normal rabbit, normal rat, rabbit anti-mammary tumor virus of RIII milk, rat anti-Gross leukemia virus, rat anti-Rauscher leukemia virus.-proteins, goat anti-rabbit-gamma-globulin, and anti-rat-gamma-globulin. The cultures were subjected to immuno-electron microscopic examinations and immunodiffusion tests. The cell lines from in vitro cultures were inoculated into four strains of mice: C57BL, Af, RIIIf, and BALB/c, having mammary tumor incidences of 0, 47, 10, and 27% respectively. A fifth mouse strain, BD2F1, was used in initial infectivity experiments. The investigation involved thin-section, whole-cell mount, and negative-strain electron microscopy. About 20-30% of the cells of both lines bore two conspicuous surface extensions, i.e, stout protrusions of varying size and shape, and microvilli. Cells cultured in vitro gradually lost their efficiency in virion production, and required passage in vivo to replenish their productivity. Intracytoplasmic A-particles exhibited three general distribution patterns: aggregated, scattered, and near the cell margin. Five modes of particle morphogenesis were observed: (1) spiked virions with nucleoids in the process of assembly, (2) spiked virions with preformed nucleoids, (3) spikeless particles with nucleoids in the process of assembly, (4) intracisternal A-particles, and (5) spikeless particles with preformed nucleoids. Only two morphologically distinct types of extracellular particles were observed: virions covered by uniformly spaced surface spikes, and virions with spikeless envelopes. Density gradient separation of B- and C-type particles was unsuccessful; the majority of the budding virions of L1210 cells prepared for immuno-electron microscopy had preformed nucleoids. Generalized leukemia occurred in 100% of the BD2F1 mice injected with cells and 47% of the BALB/c mice within 8-10 days after inoculation. However, generalized leukemia did not occur in any of the C57BL, Af, and RIIIf strains tested; the purified virions were also ineffective. The L1210(V) cell suspension lines, differing in one nutritional requirement, nonetheless produced the same types of viral particles. That the cells also gave cytoplasmic immunofluorescence when tested against the six protein antigens of Rauscher virus and demonstrated the strongest reaction to the 30,000 molecular weight protein, suggests that at least some of the viral antigens are related to Rauscher leukemia virus.

69. NEW MORPHOLOGICAL VARIANTS OF MOUSE MAMMARY TUMOUR VIRUS IN HIGH TUMOUR STRAINS OF MICE.

Chopra HC, Woodside N, Vlahakis G
Natl. Cancer Inst., Bethesda, MD 20014
Microbios; 13(51/52):41-50 1975

An electron microscopic study of the mammary tumor virus in high mammary tumor strains of mice (C3H-Avy and C3H/He) revealed new morphological variants of this agent. In one of these, there was no apparent relationship demonstrable between the intracytoplasmic type A particles and the extracellular type B virus budding from the cell surface. The latter seemed to form independently under the cell surface. The cytoplasmic type A particles acquired a coat of water soluble, dense material and an outer envelope to form a new category of intracytoplasmic type B virus particles. The envelope might be acquired from the cytoplasmic membranes or from the membranes of the cisternae. Type A particles were also observed within dense bodies, the phagolysosomes, and within the intracellular secretory ducts. These particles consisted of dense nucleoids (formed by the degradation and condensation of the inner shell of type A particles).

70. HEMIC CELL-ASSOCIATED MAMMARY TUMOR VIRUS ACTIVITY IN BALB/CF3H MICE.

Nandi S, Helmich C, Haslam S
Cancer Res. Lab., U. California, Berkeley, CA
J Natl Cancer Inst; 52(4):1277-1283 1974

Mammary tumor virus (MTV) activity in hemic cells from different sources in the BALB/cf3H mouse was studied under various experimental conditions to determine if non-nucleated reticulocytes or nucleated cells are carriers of blood-borne MTV (B-MTV). Comparisons were also made of the titer of MTV activity in hemic cells from different sources and between these cells and mammary tumor cells, which are

carriers of B-type particles. Titration of B-MTV activity in blood cells of control, hemorrhagic anemic, and hypertransfusion-induced polycythemic mice showed a lack of correlation between the numbers of circulating reticulocytes and the titer of MTV. However, the incidence of mammary nodules in polycythemic mice inoculated with mammary-tissue-borne MTV (M-MTV) was less than that of similar mice inoculated with B-MTV. Nucleated hemic cells were separated from the nonnucleated cells by selective lysis of the latter cells with NH4Cl or by immune hemolysis followed by differential centrifugation. Such cell preparations with solely or chiefly nucleated cells nevertheless contained MTV activity. These results indicate that virus activity associated with blood is carried by the nucleated cells (leukocytes and/or hematopoietic stem cells). MTV activity was detectable in nucleated hemic cells from all sources and the titer appeared less in circulating blood cells compared with those from other sources. Thus spleen and blood cells were considered the most suitable sources for B-MTV studies. MTV activity in mammary tumor cells was at least 10 times higher than in the nucleated hemic cells. However, accurate comparison was not feasible without proper identification of the cells containing B-MTV activity.

71. BIOACTIVITY AND VIRIONS IN THE BLOOD OF MICE WITH MAMMARY TUMOR VIRUS.

Moore DH, Sarkar NH, Charney J
Inst. Med. Res., Camden, N. J.
J Natl Cancer Inst; 44(4):965-973 1970

Nodule development in hormone-stimulated BALB/c female mice was used to assay blood fractions in a study of the mammary tumor virus (MTV) in the blood. Blood cells and plasma from strains RIII/Haag, A/Bi and BALB/c f. C3H/Crgl yielded endpoints (bioactivity) at dilutions no greater than 10-2, compared to 10-6 to 10-7 for RIII milk. The titer was less in plasma than in the cellular fraction. Lysed cells had bioactivity in the stroma, but not in the Hb fraction. B particles (MTV virions) were found in blood after extraction and concentration; the concentration of these particles and bioactivity varied between mouse strains and between individual mice of the same strain. Freezing and thawing markedly reduced the bioactivity of milk, bone marrow and blood cells.

72. ORGAN DISTRIBUTION OF EXOGENOUS MURINE MAMMARY TUMOUR VIRUS AS DETERMINED BY BIOASSAY.

Bentvelzen P, Brinkhof J
Radiobiological Inst TNO, Lange Kleiweg 151, Rijswijk, The Netherlands
Eur J Cancer; 13(3):241-245 1977

Cell-free mammary tumour virus activity was exhibited by extracts from the following organs of exogenously infected BALB/cfC3H mice: salivary gland, kidney, testis and epididymis. This was tested for by bioassay in female BALB/c mice, which were then forced to breed for mammary tumour production. Mammary tumour inducing activity was demonstrated for intact cells of thymus, spleen, bone marrow and liver. Radiation (3000 rad) largely destroyed the cell-bound viral activity. No cell-free or cell-bound activity was found in lung, brain or pancreas. Epigenetic factors seem to have a great influence on the expression of exogenous mammary tumour virus. (27 Refs) (Author Abstract)

73. SOME PHYSICAL AND BIOLOGICAL CHARACTERISTICS OF THE MOUSE MAMMARY TUMOR VIRUS.

Moore DH, Sarkar NH, Charney J, Kramarsky B
Inst. Med. Res., Camden, NJ
Cancer Res; 33(1):5-10 1973

Mammary tumor virus (MTV) was separated from a sample of RIII mouse milk on density gradients made of different materials. Titrations of infectivities, the isopycnic densities, and the appearance of MTV virions after fractionation are reported. Neither the infectivity nor the morphology of the MTV was appreciably affected by abrupt dilutions from strong solutions of cesium chloride, sodium chloride, or sodium iothalamate. It was not necessary to use solutions of low osmotic activity in the purification of this virus by density gradient centrifugation. In sucrose, sodium iothalamate, potassium tartrate, or citrate, the buoyant density of the main virion band was 1.18 g/ml; in cesium chloride, it was approximately 1.22 g/ml. A correlation was found between the apparent integrity of particles and their infectivity in bands recovered from various gradients. The infectivity titer of the main virion band varied with the gradient medium used; but sucrose, cesium chloride, Ficoll, potassium tartrate, or citrate and sodium iothalamate all were satisfactory, sucrose probably being preferred. The distribution and appearance of bands varied greatly from one gradient to another. Gradients of neutralized sodium phosphotungastage destroyed both the infectivity and the morphological integrity of the virions.

74. ISOPYCNIC ZONAL CENTRIFUGATION AND CHARACTERIZATION OF THE MOUSE MAMMARY TUMOR VIRUS (MTV) IN DIFFERENT GRADIENT SOLUTIONS.

Manning JS, Hackett AJ, Cardiff RD, Mel HC, Blair PB
U. California Cancer Res. Genet. Lab., Berkeley
Virology; 40(4):912-919 1970

Isopycnic zonal centrifugation and characterization of the mouse mammary tumor virus (MTV), taken from MTV-infected milk, in different gradient solutions revealed increased UV absorbance and MTV B-particle antigenicity. The isodensities of MTV were comparable to those of other RNA tumor viruses. Two distinct light-scattering bands were formed by centrifugation of MTV-positive preparations in preformed sucrose- or K tartrate-containing gradients. Only those bands at the higher buoyant density contained characteristic MTV particles; the bands of lower isodensity consisted of virus-like particles of varying size and shape (possibly incomplete MTV particles). MTV-free milk samples did not show light-scattering bands nor virus-like particles.

75. BIOLOGIC CHARACTERISTICS OF SOME MOUSE MAMMARY TUMOR VIRUSES.

Moore DH, Holben JA, Charney J
Institute for Medical Research, Copewood Street, Camden, N.J. 08103
J Natl Cancer Inst; 57(4):889-896 1976

The mammary tumor virus (MuMTV) in the milks of 7 mouse strains and substrains was titrated for infectivity in 4 strains. The data indicated that: 1) Each strain shed a different MuMTV and some genetic strains carried two MuMTV's, each discernible by its mouse strain preference in infectivity tests. 2) Less than 5% of RIIIf and about 10% of Af mice shed detectable MuMTV antigen in their milks after the third parturition. After the sixth parturition, 33% of RIIIf and 50% of Af, and after the ninth parturition, 60% of RIIIf and 90% of Af mice shed viral antigen in their milks. The MuMTV's in milks of high-parity mothers were most infectious in mouse strains different from those most susceptible to MuMTV in

RIII and A milks of low-parity mothers. Therefore, RIII and A mice each harbored two viruses, one that was removed by foster-nursing and the other that was not. 3) The susceptibility incidence of RIIIfC57BL mice to RIII virus changed gradually from about 10% in 1970 to about 70% in 1975. Susceptibility of C57BL mice to RIII virus did not change appreciably over this period, and the natural tumor incidence in RIIIfC57BL remained unchanged (about 10%). In addition to their susceptibility to RIII virus, C57BL mice were also susceptible to GR virus; they were relatively resistant to other strains tested. They were especially resistant to RIIIf virus, to which Af and BALB/c mice were very susceptible. 4) Approximately 90% of C3HfC57BL and C3HfBALB/c mice shed antigen in their milks after the third parturition, although the tumor incidence was less and occurred later than in C3H mice. No clear-cut differences could be detected in infectivities between low-parity C3H milk and high-parity C3Hf milks tested in several assay strains. (Author Abstract)

76. THE PRESENCE AND EXPRESSION OF RNA TUMOR VIRUS GENES IN NORMAL AND INFECTED CELLS: DETECTION BY MOLECULAR HYBRIDIZATION.

Bishop JM, Jackson N, Levinson WE, Medeiros E, Quintrell N, Varmus HE
Dept. Microbiol., U. of California, San Francisco
Am J Clin Pathol; 60(1):31-43 1973

Three molecular probes were used to detect genes of the Rous sarcoma virus and mouse mammary tumor virus in normal and infected cells. Using the 70S RNA of the viral genomes and the single- and double-stranded DNA transcribed from viral RNA by RNA-directed DNA polymerase, it was found that multiple copies of viral genes may be present in the DNA of ostensibly normal cells. However, the infection and transformation of mammalian (mouse and rat) cells by Rous sarcoma virus is accompanied by the appearance of virus-specific nucleotide sequences in the nuclear DNA of the host cells. The expression of Rous sarcoma virus and mouse mammary tumor virus genes in normal and infected cells was measured by RNA-DNA hybridization. Virus-specific RNA is present in both normal and transformed cells which produce neither virus nor detectable viral proteins. These data indicate that the expression of viral genes may not be controlled exclusively by the regulation of transcription.

77. TITRATIONS OF VARIOUS MOUSE MAMMARY TUMOR VIRUSES IN DIFFERENT MOUSE STRAINS.

Moore DH, Charney J, Holben JA
Inst. Med. Res., Camden, N. J.
J Natl Cancer Inst; 52(6):1757-1761 1974

Milks from the high-mammary-tumor mouse strains A, BALB/cfC3H, RIII, and C3H were titrated for infectivity in low-mammary-tumor strains C57BL/c, Af, and RIIf. 1) There was a wide variation in susceptibility of different mouse strains to the same virus; 2) the susceptibility of each mouse strain depended on the donor virus; i.e, mice resistant to mammary tumor virus from one strain were susceptible to virus from another strain; 3) RIIIf mice were relatively resistant to the virus from the parent isogenic RIII strain; 4) infectivity maxima of milks ranged from dilutions of 10-3 to 10-6. In another experiment, C57BL, BALB/c, Af, and RIIIf mice were inoculated with pooled RIIIf milk and observed for 26 months to record tumor incidence. Incidence ranged from 0% in C57BL to 97% in BALB/c mice.

78. CHARACTERIZATION OF MOUSE MAMMARY TUMOR VIRUSES PROPAGATED IN HETEROLOGOUS CELLS.

Howard DK, Colcher D, Teramoto YA, Young JM, Schlom J
Meloy Labs., Springfield, VA 22151
Cancer Res; 37(8,part1):2696-2704 1977

Mouse mammary tumor viruses (MMTV) from three different strains of mice (C3H, RIII, and GR) were used to establish productive infections in feline and mink cell lines. The virions released by these cells competed completely in a radioimmunoassay for the major virion surface glycoprotein of MMTV (gp52), demonstrating that antigenic determinants of gp52 are viral-coded. Competitive molecular hybridization experiments indicated that the 60S-70S RNA's of MMTV's propagated in feline cells contained all the nucleic acid sequences found in 60S-70S RNA from MMTV synthesized by murine cells. The virion buoyant densities in sucrose and cesium chloride, virion sedimentation coefficient, divalent cation requirement of the virion DNA polymerase, and morphology of MMTV's synthesized in the heterologous cells were similar to those of MMTV's grown in murine cells. Cultures of MMTV-infected feline cells continuously released 0.1-1.0 ug virus/10^7 cells/day during the 60-wk observation period. No detectable feline or murine C-type viruses were produced by these cultures. The synthesis of MMTV by heterologous cells provides a source of MMTV free of contaminating murine cellular nucleic acids and antigens that should be useful in immunological and molecular biological studies. (28 Refs)

79. STUDIES ON MOUSE MAMMARY TUMOR VIRUS (MTV) AND MOUSE LEUKEMIA VIRUS (MULV) BY IMMUNOELECTRON MICROSCOPY.

Shigematsu T, Dmochowski L, Williams WC
M. D. Anderson Hosp. Tumor Inst., Houston, TX
Cancer Res; 31(12):2085-2097 1971

Mouse and rat cell lines which harbored type B (mouse mammary tumor virus or MTV), type C (mouse leukemia virus or MuLV) and/or type A intracytoplasmic virus particles were reacted with each of three anti-MTV rabbit antisera and with each of two anti-MuLV anti-sera ferritin labeling in reaction mixtures was observed in immunoelectron microscope studies. Test cell lines included three mouse mammary tumor cell lines, a mouse reticulum cell sarcoma line and a rat bone tumor line. All three anti-MTV sera (designated Dmochowski, Nowinski and Verna) gave ferritin labeling of B particles in mouse mammary tumor lines; only Dmochowski serum stained C particles, but all three sera also stained A particles. Since the three sera were originally prepared against MTV from mice of different origins, the stained MTV were thought to contain common surface or membrane antigens. Absorption of anti-MTV sera with different antigenic material (including sheep erythrocytes, guinea pig kidney tissue and mammary tumor-bearing mouse embryo tissue) confirmed the specificity of ferritin labeling of B particles. Two anti-MuLV sera (designated Dmochowski and Geering) gave ferritin labeling of A and C, but not of B particles in the various cell lines. MuLV particles apparently shared common surface or membrane antigens. Absorption of antiMuLV sera with different antigenic materials confirmed the specificity of labeling of C type particles. Verna and Dmochowski anti-MTV sera showed high titers of ferritin labeling of B and A particles.

80. COMPARATIVE INVESTIGATIONS ON MAMMARY TUMOR VIRUS DETECTION IN MURINE BREAST CANCER OF STRAIN CBA/BIN.

Muller M, Zotter S, Wagner H, Grossmann H
Med. Acad. Carl Gustav Carus, Dresden, East Germany
Arch Geschwulstforsch; 38(3-4):221-231 1971

Six mammary tumors (MT) syngenically grafted into mammary tumor virus (MTV)-bearing CBA/Bln mice were investigated for their MV content. MTV-associated antigens were determined by the indirect immunofluorescent technique on frozen cut slices and by the immunodiffusion technique (micro test)using two specific rabbit anti-MTV sera. A and B particles were detected electron microscopically on ultra-thin slices. Although these methods are not directly comparable, the results obtained by the three techniques were in relatively good agreement. As determined by immunofluorescence tests, five MT contained in a rather constant manner mutually graduated amounts of MTV-associated antigens and virus particles through succeeding transplantation generations (through the 21st generation in one tumor). In the 6th passage one MT showed no demonstrable MTV following sarcomatous transformation. A sixth MT was free of any detectable virus in the first and second generations, though it had the characteristic histologic feature of other CBA MT. The immunofluorescent technique is recommended for rapid determination of the MTV content of MT.

81. FIVE-YEAR ANALYSIS OF A STRAIN OF MAMMARY ADENOCARCINOMA: MALIGNANCY, STRUCTURE, VIRAL PARTICLES.

Thomas JA, Hollande E, H y M, Jouanne C
Lab. Cell Biol., U. Paris, France
C R Acad Sci D (Paris); 277(3):381-386 1973

The T III strain of mouse mammary adenocarcinoma has been passaged for 5 yr in an inbred strain (LAB) of Swiss mice. After 92 continuous passages an average of 86.7% of the mice inoculated developed tumors which, in 14.5% of the cases, regressed. Beginning with the 20th passage tumor invasion and metastases were no longer observed, but the histological structure of these tumors has remained unchanged. Mammary tumor virus particles (A and B) were present in large numbers in the initial tumor, but C particles only formed during some stages of budding on the plasma-lemma; very few Ai particles were detected. During the first 28 passages A-particles were always present, but B, C and Ai particles were not detected in some passages. From the 42nd to the 68th passage, C-particles were present in the largest numbers and the number of Ai particles had increased. Starting with the 42nd passage, B particles disappeared, and A particles disappeared between the 77th and the 91st passages; large numbers of C particles were detected, and intracisternal Ai particles were found near C particles after the disappearance of A and B particles. Between the 30th and 89th passages hemorrhagic ascites occurred in 42 of the 316 mice which developed abdominal adenocarcinomas when injected ip with the virus. Ascites fluid was reinoculated in ten cases, and two ascites strains of T III were obtained, but only one could be passaged for any length of time. The ascites fluid contained cancer acini. C and Ai particles were present in the acini, but A and B particles had disappeared.

82. DIFFERENCES IN MOUSE MAMMARY TUMOR VIRUSES. RELATIONSHIP TO EARLY AND LATE OCCURRING MAMMARY TUMORS.

Schlom J, Colcher D, Drohan W, Kettmann R, Michalides R, Vlahakis G, Young J
NCI, Bethesda, MD 20014
Cancer; 39(6,Suppl):2727-2733 1977

The murine model has been used extensively to study the various factors involved in the etiology of mammary carcinoma. Inbred mouse strains have been classically categorized into (i) high incidence stains with tumors occurring relatively early in the life of the animal, or (ii) low or moderate incidence strains with tumors occurring later on in life. We have radioactively labeled the RNA genome of the mouse mammary tumor virus (MMTV) from each of several mouse strains. We report here, using the technique of molecular hybridization, that the class of MMTVs responsible for the early occurring mammary tumors in high incidence strains can be clearly distinguished from the MMTVs associated with late occurring mammary tumors in low or moderate incidence strains; we also demonstrate that minor differences in MMTV genomes can also exist within these classes. Our findings show that MMTVs are transmitted via the germ line (as a germinal provirus) in some mouse strains, whereas in other strains, a non-germ line transmission is clearly demonstrated. Biochemical techniques can thus be used to track the mode of transmission of oncogenic viruses. The relationship of these findings to an understanding of the etiology of mammary carcinoma is discussed. (Author abstract) (23 Refs)

83. PRODUCTION OF AN ONCORNAVIRUS BY THE CONTINUOUS HUMAN CELL LINE, DETROIT-6.

Miller GG, Zhdanov VM, Lozinksy TF, Volkova MY, Ilyin KV, Golubev DB, Irlin IS, Bykovsky AF
N. F. Gamaleva Inst. Epid. Microbiol., Moscow, USSR
J Natl Cancer Inst; 52(2):357-364 1974

An oncornavirus was discovered in a subline of the continuous human cell line, Detroit-6, established from bone marrow cells of a patient with lung carcinoma. Electron microscope studies of the cells revealed particles of types A and B or theta. The former were found in various parts of the cytoplasm, but the latter were predominantly in the intercellular spaces. Biochemical and biophysical tests were used to study both extracellular and intracellular virus. The extracellular virus bands at a density of 1.16-1.17 g/ml in sucrose gradients; production of such bands is inhibited by actinomycin D. The virions contains RNA with a sedimentation coefficient of 60-70S as well as slower sedimenting components, including 4S RNA. They possess the reverse transcriptase activity associated with 60-70S RNA. The virus was immunologically distinct from the mouse mammary tumor virus and shared a common antigen with the virus isolated from HEp-2 cells and with the rhesus monkey mammary carcinoma virus.

84. SURFACE STRUCTURE OF VIRIONS BUDDING FROM L1210(V) GLN- MOUSE LEUKEMIA CELLS.

Demsey A, Calvelli TA, Kawka D, Stackpole CW, Sarkar NH
Memorial Sloan-Kettering Cancer Center, Walker Lab., Rye, NY
Virology; 75(2):484-487 1976

The surface structure of virions budding from L1210(V) gln- murine leukemia cells a subline of L1210(V) that requires glutamine for growth was studied by freeze-drying intact cells and examining them by electron microscopy. Three labeling experiments were done using hybrid antibodies: (1) labeling for murine mammary tumor virus (MuMTV) spike glycoprotein; (2) labeling for murine leukemia virus (MuLV) knob glycoprotein; and (3) double-labeling for MuLV and MuMTV surface components on L1210(V) gln- cells. Two types of virus particles were detected, one with random 10-nanometer (nm) surface projections, similar to viruses on cells producing only MuLV, and one with regularly arranged 5-nm projections, similar to budding viruses on cells producing only MuMTV. The results of the double-labeling experiments agree with the indication that individual viral envelopes on L1210(V) gln- cell viruses are homogeneous in their surface structure. The

mechanism that draws together the surface glycoproteins during budding appears, therefore, to be highly specific. (20 Refs)

85. SURFACE STRUCTURE OF MOUSE MAMMARY TUMOR VIRUS.

Sarkar NH, Moore DH
Inst. Med. Res., Camden, NJ
Virology; 61(1):38-55 1974

The envelope of the mouse mammary tumor virus (MuMTV) was studied to determine whether the surface projections have a structural symmetry similar to that of myxo and para-myxoviruses. Viral particles were purified from mouse milk and subjected to negative staining, thin sectioning, or freeze drying followed by electron microscopy. The negatively stained and the thin sectioned specimens showed surface projections, each connected to the virion by a thin stalk and with a distal knob. The projections were arranged mostly with a sixfold symmetry, although some were arranged in fivefold symmetry. The interprojection distance was estimated to be 73.7 Angstroms. A reticular network was revealed on the viral membrane, consisting of hexagonal and pentagonal units, and to which the projections were apparently attached at the corners. Freeze drying and shadowing showed a regular array of pits on the virion surface, also in sixfold and fivefold symmetry. Interpit distance was 218 plus or minus 43 Angstroms. The pits are believed to be a unique morphological feature of the MuMTV envelope. Some hypotheses are given to explain the origin and arrangement of the pits. The results suggest that projections of enveloped viruses are more ordered structures than commonly thought. The hexagonal and pentagonal symmetries indicate that the virion is quadi-icosohedral in form, similar to a geodesic dome.

86. MOUSE MAMMARY TUMOR VIRUS (MTV). EXPERIMENTAL STUDY OF THE STRUCTURE IN THE EXTRACELLULAR STAGES. GENERAL INTERPRETATION OF THE VIRAL CYCLE.

Thomas JA, Hollande E, Henry M, Dutrillaux MC, Vilain C
Ctr. Cell Physiol. Biol. Lab., Paris
C R Acad Sci D (Paris); 270(19):2387-2390 1970

In the extracellular phase of the viral cycle of mouse mammary tumor virus (MTV) in the milk and tumor tissue of infected Swiss mice, the internal layer of the viral envelope proved to be a sort of basic armature, composed, at least in part, of lipoproteins. Multiple spicules were attached to it from the outside of the viral body; the helicoidal filament of the nucleocapsid, composed of ribonucleoprotein, was attached to it from the inside, by means of one face of an interposing membrane. Following dehiscence of the envelope, this membrane became itself an envelope for the freed nucleocapsid (Br). The spicules detached themselves from the mature viral particle (Bm) at this time, agglutinated spontaneously for a short time (sometimes into large masses) and then dispersed, leaving the viral body glabrous in an action which could be initiated experimentally by pepsin hydrochloride or ethylenediaminetetracetate (EDTA). EDTA was also capable of initiating dehiscence of the viral envelope (as were phospholipase A and D) and of creating a swelling of the membrane enclosing Br, carrying inflation to the point of rupture and expulsion of the nucleocapsid and its content in the form of tufts, plumes, and masses of varying sizes. In addition to Br, which were found within a few min of beginning nursing, intact Bm were also found in extracts of milk coagulated in the stomachs of nursing mice. These Bm appeared to be still intact one-half hour after their intubation into the stomachs of adult mice.

87. DEMONSTRATION OF NEW STAGES IN THE EVOLUTION OF MAMMARY TUMOR VIRUS IN THE MOUSE: INTRACYTOPLASMIC VIRAL INFRAPARTICLES AND THE FORMATION OF PARTICLE A.

Thomas JA, Hollande E, Henry M, Dutrillaux-Ducros MC
Ctr. Cell Physiol., Paris
C R Acad Sci D (Paris); 270(3):574-577 1970

Electron microscopy of 630 sections of spontaneous mammary tumor or tumor appearing after inoc of Swiss mice with MTV virus disclosed the presence of intracytoplasmic infraparticles in 6 developmental stages, culminating in one which closely resembled viral particle A. Stage I consisted of a dense central nodule (approx diameter, 140 angstroms) surrounded by a clear space delimited by a discontinuous, granular corona (approx diameter, 580 angstroms). The adjoining hyaloplasm was disposed in what appeared to be numerous, arching bridges, the whole attaining a diameter of greater than 2300 angstroms. In Stage II, these "bridges" were reduced in number and size and assumed a more radial distribution, while the central nodule, appearing to be breaking up, was still attached to the corona by a curving stream of granules. In Stage III, the central nodule (approx diameter, 330 angstroms) was surrounded by a clear space, the delimiting corona was less discontinuous and more dense. In Stage IV, a clear central zone with some residual dark granules was surrounded by a continuous, irregular corona (approx diameter, 610 angstroms) whose internal surface appeared to hold the material which had formed the central nodule of the previous stages. In Stage V, the clear zone and its corona were surrounded by 2 concentric, annular zones (dense and relatively clear, resp). In Stage VI, these annular zones were clearly individualized. At this stage, as compared to viral particle A, the central zone is somewhat more dense, the corona somewhat less regular, and the overall size somewhat smaller.

88. THE STRUCTURE OF THE MOUSE MAMMARY TUMOR VIRUS: ISOLATION AND CHARACTERIZATION OF THE CORE.

Teramoto YA, Cardiff RD, Lund JK
Dept. Pathology, Sch. Medicine, Univ. California, Davis, CA 95616
Virology; 77(1):135-148 1977

A method was developed that reproducibly provides significant quantities of biophysically, biochemically, and morphologically identifiable mouse mammary tumor virus (MMTV) cores. Treatment of MMTV virions with nonionic detergents resulted in the release of RNA particles of 1.24-1.26 g/cm^3 density. Pretreatment with 0.5% TX-100 for 15 min at 37 C prior to isopycnic centrifugation resulted in max recoveries of 40%-60% MMTV cores. These particles were morphologically identical to the internal core structure of MMTV virions and contained 60S-70S RNA and reverse transcriptase. The antigenic composition of MMTV was examined by immunodiffusion and by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The major polypeptides of the cores were p30, p28, and p14. Envelope glycoproteins could not be identified among any of the many minor polypeptides. (26 Refs)

89. HOST CELL FACTORS IN THE SURFACE OF THE MOUSE MAMMARY TUMOR VIRUS (MEETING ABSTRACT).

Sheffield JB, Lasfargues EY, Taraschi N, Daly TM
Inst. Medical Res., Camden, NJ 08103
J Cell Biol; 70(2/Part2):82a 1976

There currently exist two major sources for the Mouse Mammary Tumor Virus (MuMTV): 1) the milk of strains with

high tumor incidence, and 2) fluids obtained from primary or continuous cultures derived from mammary tumors. We have compared viruses obtained from these sources using freeze-etch electron microscopy, SDS-PAGE, and surface labeling with lactoperoxidase and iodine or with galactose oxidase-borotritide. We have also examined materials found in virus-free mouse milk. All of the viruses examined shared gp90, gp55, p42, gp38, p28, p18, and p12 (gp=glycoprotein, p=polypeptide; the number is apparent molecular weight in thousands), while milk virus contained gp140, gp68, gp34, and p14 as well. Vesicular material from virus-free milk contained gp140, gp68, and p14 as well as other high molecular weight materials. Surface labeling studies of the tissue culture virus indicated that the polysaccharide portion of gp55 and gp38 were accessible, but the only accessible protein was that of gp55. Several proteins (gp 140, gp68, gp55) were accessible on the milk virus, but the major accessible polysaccharides were associated with gp140 and gp68, and the accessibility of the polysaccharides of gp55 and gp34 was greatly reduced. By freeze-etch electron microscopy, the outer surface of the milk virus was seen to be covered with a matrix containing a regular pattern of pits, which was absent from tissue culture virus. We conclude that the surface of MuMTV is a complex structure containing a bimolecular lipid membrane in which the protein portions of gp90 and gp38 are located. The polysaccharides of these glycoproteins extend outward. Within this polysaccharide material are the surface "spikes," gp55, which are the only true surface protein. Virus produced in the milk contains a second layer of glycoprotein gp140 and gp68, probably absorbed from the milk, which limits the accessibility of other viral polysaccharides. This layer forms the coat visualized by freeze-etching.

90. ATYPICAL C PARTICLES IN ADENOCARCINOMAS INDUCED BY IMPLANTATION OF FUKU CELLS.

Yagi MJ, Hamamoto ST, Duafala JC, Pitelka DR
Dept. Bacteriology and Immunology, Univ. California, Berkeley, Calif. 94720
J Natl Cancer Inst; 52/53(1/6):1835-1837 1974

Tumors induced in isogeneic BALB/c/Crgl mice by the murine leukemia virus (MuLV)-producing mammary tumor cell line FUKU were rapidly growing, invasive type-B adenocarcinomas. Ultrastructural examination of the tumors revealed intracytoplasmic A particles; budding, immature, and a few mature C particles; and rare mature B particles. Most budding and immature particles had surface spikes typical of mammary tumor virus B particles, despite the infrequency of mature forms. Most mature virions were atypical, with nucleoids characteristic of mature MuLV C particles and with B-particle surface spikes.

91. APPLICATION OF FREEZE-DRYING INTACT CELLS TO STUDIES OF MURINE ONCORNAVIRUS MORPHOGENESIS.

Demsey A, Kawka D, Stackpole CW
Memorial Sloan-Kettering Cancer Center, Walker Laboratory, Rye, New York 10580
J Virol; 21(1):358-365 1977

Using a method for freeze-drying intact cells, uninfected and murine leukemia virus (MuLV)-infected JLSV9 cell surfaces, as well as murine mammary tumor virus (MuMTV)-infected cell surfaces, were examined by electron microscopy. The 10-nm knobs of MuLV and the 5-nm spikes of MuMTV were clearly revealed on the surfaces of budding viruses and were also found dispersed over the cell surface. The MuLV knobs are randomly arranged on the virus surface, whereas the MuMTV spikes are much more ordered. Because freeze-fractured budding viral envelopes are devoid of intramembranous particles, the observed surface particles do not appear to be merely accentuated intramembranous particles. This technique should permit further analysis of the morphogenesis of viral envelopes without the need for externally applied labels. (Author Abstract)

92. THE MORPHOLOGY OF MURINE ONCORNAVIRUSES FOLLOWING DIFFERENT METHODS OF PREPARATION FOR ELECTRON MICROSCOPY.

Sarkar NH, Manthey WJ, Sheffield JB
Inst. Med. Res., Camden, N.J.
Cancer Res; 35(3):740-749 1975

The effects of various preparative procedures in neutralizing the effects of osmotic pressure and surface tension for murine leukemia and mammary tumor viruses were studied by electron microscopy. Fixing in glutaraldehyde , gradual dehydration in alcohol and water mixtures followed by air-drying from alcohol, and critical-point drying were the techniques studied, both alone and in combination. Metal shadowing techniques were used to analyze the three-dimensional aspects of particle morphology. Both the tumor and leukemia viruses appeared in head-and-tail forms, with a peak head diameter of 122 and 130 nm, respectively, using conventional negative staining procedures with neutral sodium phosphotungstate . Round virions with peak diameters of 148 and 130 nm, respectively, were obtained with negative staining with uranyl acetate . Virus pre-fixed in uranyl acetate gave peak diameters of 143 and 123 nm. A combination of glutaraldehyde fixation, gradual dehydration, and critical-point drying in CO2 preserved the spherical shape of viruses and produced peak diameters of 99 and 82 nm, respectively. Except under conditions of negative staining with phosphotungstate, the mammary tumor virus was always larger than the leukemia virus. Metal shadowing of virus particles showed flattening, except with critical-point drying. No shadow was made by negatively-stained particles. Alterations in osmotic strength from hypotonic to isotonic sucrose solutions enabled conversion of virus from spherical to head-and-tail forms. It is concluded that a combination of all three treatments, preferably with uranyl acetate staining, yields spherical virus morphology with minimum distortion.

93. A DETERMINATION OF THE OUTER DIMENSIONS OF ONCORNAVIRUSES BY SEVERAL ELECTRON MICROSCOPIC PROCEDURES.

Luftig RB, McMillan PN, Culbreth K, Bolognesi DP
Worcester Fdn. Exp. Biol., Shrewsbury, Mass.
Cancer Res; 34(7):1694-1706 1974

The effect of negative stain, freeze-fracture, and thin-sectioning procedures on the size of several oncornaviruses was determined. The estimated size ranges for three classes of oncornaviruses are: (a) 1250 to 1450 Angstrom, for avian C-type viruses (avian myeloblastosis virus (AMV) and Rous sarcoma virus, Prague strain); (b) 1350-1550 Angstroms, for murine C-type viruses (friend leukemia virus (FLV) and Moloney leukemia virus); and (c) 1200-1400 Angstroms, for B-type viruses (mouse mammary tumor virus). Concomitant studies of oncornavirus cores indicated a clear difference between avian and murine type viruses. AMV cores measured about 730 Angstrom in diameter and had a ribonucleoprotein component that was centrally collapsed. FLV cores in contrast measured about 840 Angstrom and appeared to have the ribonucleoprotein closely associated with the core shell. These results suggest that the 100-Angstrom smaller value obtained for the outer dimension of avian viruses is due to the presence of a smaller core component.

94. ULTRASTRUCTURAL COMPARISON OF A VIRUS FROM A RHESUS-MONKEY MAMMARY CARCINOMA WITH FOUR ONCOGENIC RNA VIRUSES (MEETING ABSTRACT).

Kramarsky B, Sarkar NH, Moore DH
Inst. Med. Res., Camden, N.J.
Proc Natl Acad Sci USA; 68(7):1603-1607 1971

The ultrastructure and morphogenesis of Mason-Pfizer monkey virus (M-PMV), isolated from a mammary carcinoma in a Rhesus monkey, was compared with those of murine mammary tumor virus (MuMTV), murine leukemia virus (MuLV), L1210 leukemia-associated virus, and avian myeloblastosis virus. The simian virus resembled MuMTV and the L1210 virus in that it produced intracytoplasmic particles that were enveloped during budding. It resembled L1210 virus and MuLV in budding with smooth envelopes. It differed from all the others in being more fragile. This fragility is probably due to an inherent tendency of the supercoiled nucleocapsid to unwind, exerting a pressure upon the virion envelope. The similarities suggest that the monkey virus is an oncogenic virus.

95. RELATIONSHIP BETWEEN HYDRATION AND PROTON NUCLEAR MAGNETIC RESONANCE RELAXATION TIMES IN TISSUES OF TUMOR-BEARING AND NON-TUMOR-BEARING MICE: IMPLICATIONS FOR CANCER DETECTION.

Hazlewood CF, Cleveland G, Medina D
Baylor Coll. Med., Houston, Tex.
J Natl Cancer Inst; 52(6):1849-1853 1974

Hyperplastic alveolar nodule outgrowth lines with mammary tumor-producing capability were transplanted into the inguinal mammary gland-free fat pads of syngeneic 3-wk-old BALB/c females. Mammary tumors from C3H and C3Hf mice were transplanted sc into 4-month-old syngeneic females near the right axilla. Preneoplastic mammary nodule tissue and mammary neoplasms could be distinguished from normal murine pregnant mammary tissue by nuclear magnetic resonance (NMR) relaxation times (T1 and T2) and diffusion coefficient of water protons. The presence of a growing mammary tumor in the host altered the T1 and T2 of water protons in other organs such as spleen and kidneys. These changes in T1 and T2 were independent of changes in organ hydration. The presence of an oncogenic mammary tumor virus in C3H mice also significantly influenced the T1 and T2 of water protons in some organs. These data strongly suggest that the water-macromolecular interactions in tissues are altered by several different factors (i.e, the presence of a tumor or virus in the host) and are not strictly correlated with tissue hydration. The data suggest that NMR spectroscopy may be useful in cancer research and cancer detection.

96. COMPARISONS BETWEEN DIAMETERS MEASURED BY LASER BEAT FREQUENCY SPECTROSCOPY (LBFS) AND BY ELECTRON MICROSCOPY FOR MURINE MAMMARY TUMOR (MUMTV), ROUS SARCOMA (RSV), AND FELINE LEUKEMIA (FELV) VIRUSES (MEETING ABSTRACT).

Salmeen I, Rimai L, Luftig RB, Liebes L, McCormick JJ
Res. Staff, Ford Motor Co., Dearborn, MI 48121
Biophys J; 16(21-part2):178a 1976

The variance in the distribution of diameters of RNA tumor viruses measured in electron micrographs is 10%-20% of the mean. LBFS of solutions with such particle size distributions would yield approximately single exponential correlation functions with time constants corresponding to light scattering intensity weighted average hydrodynamic diameters (dh). If the electron micrographs (e m) represent solution size distributions, then dh should be compared not with the arithmetic mean (the usual way to report e m diameters), but with the light scattering intensity weighted average (diw) of the e m distribution. DH was measured for murine mammary tumor virus (MuMTV), Rous sarcoma virus (RSV), and feline leukemia virus (FeLV), on samples purified by density gradient centrifugation followed by dialysis into phosphate buffer and ultracentrifugation in order to clear particles with sedimentation coefficients greater than that of the single virions. Catalase crystal calibrated e m were obtained on FeLV both before and after, and on RSV and MuMTV only before the final ultracentrifugation. Whereas the arithmetic mean of the e m size distributions are at least 10% smaller than dh, the calculated diw (using Mie theory to estimate relative scattering intensities) agreed to within experimental error with dh diw (nm) are: 147+-3 (MuMTV), 139+-3 (RSV), 161+-5 (FeLV). This agreement suggests that the e m size distributions are representative of the size distributions in solution. (No refs)

97. DIFFUSION AND ELECTROPHORESIS OF RNA TUMOR VIRUSES.

McCormick JJ, Rich MA, Liebes L, Rimai L, Salmeen I
MI Cancer Found, Detroit, MI 48201
Proc Am Assoc Cancer Res; 16:152 1975

The development of laser beat frequency spectroscopy (LBFS) has enabled the rapid and accurate measurement of certain physical parameters from nondestructive characterization of viruses in solution. We have used LBFS to measure the diffusion constant of a number of RNA tumor viruses. Assuming that these viruses are spherical, we calculated the hydrodynamic diameter of these viruses using the Stokes-Einstein equation. We found that diameter (plus or minus 5%) to be 189 nm for RSV, 197 nm for RAV, 190 nm for MuMTV, 197 nm for FeLV, 138 nm for AMV, and 146 nm for MuLV (Rauscher). We also examined the diameter of MuMTV and AMV as a function of pH. At the following pH values, the respective diameters for MuMTV and AMV were: pH 7.0, 190 nm, 138 nm, pH 5.0, 290 nm and 156 nm. By means of electrophoretic light scattering, we have determined the electrophorectic mobility of several viruses. The mobility values for MuMTV and AMV in cm^2/V sec X 10**-4 at pH 7 are respectively -3.2 and -2.8 and at pH 5 are -2.0 and -2.4. (Author Abstract)

98. HYDRODYNAMIC DIAMETERS OF MURINE MAMMARY, ROUS SARCOMA, AND FELINE LEUKEMIA RNA TUMOR VIRUSES: STUDIES BY LASER BEAT FREQUENCY LIGHT-SCATTERING SPECTROSCOPY AND ELECTRON MICROSCOPY.

Salmeen I, Rimai L, Luftig RB, Liebes L, Retzel E, Rich M, McCormick JJ
Scientific Research Laboratories, Ford Motor Company, Dearborn, Michigan 48121; Worcester Foundation for Experimental Biology, Shrewbury, Massachusetts 01545; and Michigan Cancer Foundation, Detroit, Michigan 48201
J Virol; 17(2):584-596 1976

We have studied purified preparations of murine mammary tumor virus (MuMTV), Rous sarcoma virus (RSV; Prague strain), and feline leukemia virus (FeLV) by laser beat frequency light-scattering spectroscopy, ultra-centrifugation, and electron microscopy. The laser beat frequency light-scattering spectroscopy measurements yield the light-scattering intensity, weighted diffusion coefficients. The corresponding average hydrodynamic diameters, as calculated from the diffusion coefficients by the Stokes-Einstein equation for MuMTV, RSV, and FeLV, respectively, are: 144 plus or minus 6 nm, 147 plus or minus 7 nm, and 168 plus or minus 6 nm. Portions of the purified RSV and MuMTV preparations, from which light-scattering samples were obtained, and

portions of the actual FeLV light-scattering samples were examined by negatively stained, catalase crystal-calibrated electron microscopy. The light-scattering intensity weighted averages of the electron micrograph size distributions were calculated by weighting each size by its theoretical relative scattering intensity, as obtained from published tables computed according to the Mie scattering theory. These averages and the experimentally observed hydrodynamic diameters agreed to within plus or minus 5%, which is the combined experimental error in the electron microscopic and light-scattering techniques. We conclude that the size distributions of singlet particles observed in the electron micrographs are statistically true representations of the sedimentation-purified solution size distributions. The sedimentation coefficients ($s_{20,w}$) for MuMTV, RSV, and FeLV, respectively, are: 595 plus or minus 29S, 689 plus or minus 35S, and 880 plus or minus 44S. Virus partial specific volumes were taken as the reciprocals of the buoyant densities, determined in sucrose density gradients. The Svedberg equation was used to calculate particle weights from the measured diffusion and sedimentation coefficients. The particle weights for MuMTV, RSV, and FeLV, respectively, are: (3.17 plus or minus 0.32) x 10^7, (4.17 plus or minus 0.42) x 10^7, and (5.50 plus or minus 0.55) x 10^7 daltons.

99. MAMMARY-TUMOR VIRUS ACTIVITY IN BRAIN AND LIVER OF GR STRAIN MICE.

Bentvelzen P, Daams JH
Netherlands Cancer Inst., Amsterdam
Eur J Cancer; 6(9):273-276 1970

Cell-free extracts of liver and brain of mice (GR strain) carrying mammary tumors induced by mammary tumor virus were injected ip into young BALB/c mice (0.5 ml/mouse), and blood from tumor-bearing mice was similarly injected into test mice (0.1 ml/mouse), to investigate the incidence of tumors in injected mice of various strains. Only 1 out of 81 forced-bred mice of the BALB/c strain developed a mammary tumor before attaining 1 yr-of-age in control animals, but extracts from livers and brains induced 35 and 29% mammary tumors, resp, in these mice. Brain and liver extracts from other mouse strains which carry mammary tumor virus (C3H strain, BALB/cfC3H strain, and BALB/cfGR strain) caused no tumors. Whole blood of mammary tumor virus-carrying mouse strains BALB/cfC3H and BALB/cfGR induced mammary tumors in recipient mice (tumor incidence of 75-90%), while blood from virus-carrying strain C3H mice caused only 25% tumor incidence. Liver, brain and blood of virus-carrying GR mice appears to contain a biologically active form of the mouse mammary tumor virus.

III. FACTORS INFLUENCING MuMTV EXPRESSION

A. Hormonal Control of MuMTV Expression In Vitro

100. PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS BY CULTURED CELLS IN THE ABSENCE AND PRESENCE OF HORMONES: ASSAY BY MOLECULAR HYBRIDIZATION.

Ringold G, Lasfargues EY, Bishop JM, Varmus HE
Dep. Microbiol., Univ. California, San Francisco, CA
Virology; 65(1):135-147 1975

The regulation of mouse mammary tumor virus (MMTV) gene expression was studied by measuring the production of virus and the transcription of viral genes in cultured cells. MMTV from the milk of RIII mice was used. A new assay based on the hybridization of labeled virus-specific DNA (cDNA) with RNA extracted from virus released into the growth medium was used to measure virus production. Levels of virus-specific RNA in various cells were measured by annealing MMTV cDNA with cell RNA. In cell lines and primary explants derived from mammary tumors of several strains of mice the amount of virus production correlates with the level of virus-specific RNA. Experiments with dexamethasone (a synthetic glucocorticoid) support the suggestion that transcriptional controls are of primary importance in regulating the production of MMTV in these cells. Cells treated with the hormone show parallel increases in virus production and intracellular virus-specific RNA. In contrast, a lymphoma cell line (S49) derived from a lymphoma induced by mineral oil in a BALB/c mouse contains large quantities of MMTV-specific RNA yet produces extremely low levels of virus. In these cells, mechanisms other than transcriptional controls may be important in regulating virus production.

101. LEVELS OF MAMMARY TUMOR VIRUS IN HORMONE-DEPENDENT AND -INDEPENDENT MOUSE MAMMARY TUMOR CELLS.

Sluyser M, Nouwen T, Hilgers J, Calafat J
Div. Endocrinology, Netherlands Cancer Inst., Antoni von Leeuwenhoek-Huis, Amsterdam, Netherlands
Cancer Res; 37(7):1988-1990 1977

Levels of mammary tumor virus particles (types A and B) and virus antigen were assayed in hormone-dependent and -independent mammary tumors of GR mice. Various transplant generations of seven separate tumor lines were investigated. The results indicated that the tumors consisted of different cell clones, each of which exhibited a separate progressive expression and subsequent loss of the mammary tumor virus. When the tumors were transplanted, levels of B particles first declined in the hormone-dependent cells. In later transplant generations, however, the B particle content of the autonomous cells also dropped. In some tumor lines, this was accompanied by a decrease in viral antigens and/or A particles; in other lines these concentrations remained high. One tumor line (line V), which remained hormone-dependent throughout nine transplantations, was practically devoid of B particles but contained high levels of A particles and mammary tumor antigen. (13 Refs)

102. CONDITIONS FOR OPTIMAL MTV SYNTHESIS IN VITRO AND THE EFFECT OF STEROID HORMONES ON VIRUS PRODUCTION.

Dickson C, Haslam S, Nandi S
Dept. Zool., Univ. California, Berkeley
Virology; 62(1):242-252 1974

The DNA polymerase assay was used with synthetic template/primers to measure the synthesis of mouse mammary tumor virus (MTV) obtained from the tissue culture fluid of primary mouse mammary tumor cells in vitro. A high level of DNA polymerase activity was obtained with the synthetic template/primer rA:dT10 and a low level was obtained with dA:dT10. The DNA polymerase activity was associated with particles exhibiting the physical, morphological, and immunological properties of MTV; there was a linear relationship to protein concentration up to 40 microg/ml. A high cell seeding density was required for optimal MTV synthesis, and synthesis was stimulated by a variety of steroid hormones; dexamethasone was the most potent, followed by hydrocortisone, corticosterone, aldosterone, and deoxycorticosterone. In the presence of fetal calf serum, insulin had a slight stimulatory effect. An increase in the rate of MTV synthesis was detectable 8-10 hr after exposure of the cells to hydrocortisone or other steroid hormone systems; these systems had no detectable effects on the overall rate of DNA, RNA, or protein synthesis. The results suggest that the rate of

MTV synthesis is controlled via a receptor mechanism acting either indirectly on a critical cell function required for MTV synthesis or directly on an integrated viral genome.

103. TUMOR-PRODUCING CAPABILITIES OF HYPERPLASTIC ALVEOLAR NODULES IN VIRGIN AND HORMONE-STIMULATED BALB/C F. C3H AND C3HF MICE.

Medina D, DeOme KB, Young L
Baylor U. Coll. Med., Houston, Tex.
J Natl Cancer Inst; 44(1):167-174 1970

Hyperplastic alveolar nodules (HAN) developed sporadically and infrequently in mammary tumor virus-positive BALB/c f. C3H virgin female mice, beginning at 35 weeks of age, and more frequently in nodule-inducing virus-positive C3Hf virgin female mice, beginning at 82 weeks of age. Hormone stimulation by pituitary isografts led to the appearance of HAN after 2 mo of stimulation in BALB/c f. C3H mice and after 6 mo of stimulation in C3Hf mice. HAN isologously transplanted into 3-week-old mice of either strain from virgin and hormone-stimulated mice did not differ in their capacity to induce tumors. In BALB/c f. C3H, but not C3Hf mice, hormone stimulation of the host receiving an isologous nodule transplant decreased the mean latent period of tumorigenesis, but did not influence the ultimate tumor incidence.

104. GLUCORTICOID-STIMULATED ACCUMULATION OF MOUSE MAMMARY TUMOR VIRUS RNA: INCREASED RATE OF SYNTHESIS OF VIRAL RNA.

Ringold GM, Yamamoto KR, Bishop JM, Varmus HE
Dept. Biochemistry, Univ. California, San Francisco, San Francisco, CA 94143
Proc Natl Acad Sci USA; 74(7):2879-2883 1977

Glucocorticoid hormones specifically increase the intracellular concentration of mouse mammary tumor virus (MMTV) RNA in a cultured cell line from a GR mouse mammary carcinoma (GR) and in an MMTV-infected rat hepatoma cell line (M1.19). In contrast, these steroids have no effect on the concentration of MMTV RNA in a lymphoma line, S49, from a BALB/c mouse. Using a molecular hybridization procedure to detect newly synthesized RNA, we have directly measured the effect of dexamethasone, a synthetic glucocorticoid, on the rate of MMTV RNA synthesis. In GR cells the hormone causes a 10-fold increase in the rate of synthesis of viral RNA without appreciably affecting the overall rate of cellular RNA synthesis. The transition from the basal to the maximally stimulated rate of MMTV RNA synthesis occurs within the earliest labeling period, 0-15 min after addition of the hormone. Thus, it appears that glucocorticoids regulate MMTV genes principally by this rapid and specific alteration of their rate of transcription. Similar results are obtained in M1.19 rat hepatoma cells. In contrast, dexamethasone does not affect the rate of viral RNA synthesis in S49 lymphoma cells. (Author abstract) (31 Refs)

105. STEROID INDUCTION OF MOUSE MAMMARY TUMOR VIRUS: EFFECT UPON SYNTHESIS AND DEGRADATION OF VIRAL RNA.

Young HA, Shih TY, Scolnick EM, Parks WP
Laboratory of Tumor Virus Genetics, National Cancer Institute, Bethesda, Maryland 20014
J Virol; 21(1):139-146 1977

Steroid hormones have been demonstrated to induce in tissue culture the production of mouse mammary tumor viral (MMTV) RNA, proteins, and particles 10-fold compared with constitutive levels. However, previous data of increased viral RNA levels did not distinguish between an increased rate of viral-specific RNA synthesis and a slower rate of viral RNA degradation. According to the recently developed assay of Coffin et al (1974) for measuring rates of viral RNA synthesis, short-term labeling experiments of a mouse mammary tumor cell line indicate that the glucocorticoid hormone dexamethasone stimulates a 3-fold increase in the synthesis of MMTV-specific RNA within 10 min after the addition of hormone and that stimulation of RNA synthesis reaches 5- to 10-fold within 30 to 60 min, while the synthesis of Moloney leukemia virus-specific RNA in the same cell is unaffected by steroids. The decay rates of pulse-labeled and accumulated MMTV RNA in the presence or absence of dexamethasone show this RNA to have a half-life of greater than 8 h. In addition, hormone-stimulated MMTV RNA appears to have an increased rate of decay compared to basal MMTV RNA, thus ruling out an increased stability of MMTV RNA in the presence of steroid hormones as the basis for increased RNA levels. Thus, the magnitude, rapidity, and specificity of hormone action on MMTV RNA synthesis indicate a primary effect upon transcription. (Author Abstract)

106. HIGH FREQUENCY VARIATION IN MAMMARY TUMOR VIRUS EXPRESSION IN CELL CULTURE.

Parks WP, Hubbell ES, Goldberg RJ, O'Neill FJ, Scolnick EM
Natl. Cancer Inst., Bethesda, MD 20014
Cell (Camb); 8(1):87-93 1976

In studying variation in viral expression in cell cultures, it was found that clonal derivatives of C3HMT murine mammary cell lines in culture demonstrated conversion of mammary tumor virus (MMTV) expression at a rate of approximately 6 per 100 clones. This alteration was largely unidirectional from a relatively high level (MMTVH) to a 10-fold lower level (MMTVL). This high rate of MMTVL variant conversion was in contrast to the mutational rate (approximately 3/million cells) that governs development of resistance to 6-thioguanine (TG) in the same mammary cells. In somatic cell hybrids between different MMTV TG resistance clones and mouse or hamster TK- cells, expression of constitutive levels of MMTV and responsiveness to dexamethasone induction was dominant. Thus MMTV expression was regulated by at least two levels of positive control, CIS-dominant constitutive expression and glucocorticoid stimulation, but the former was subject to a high rate of variant formation.

107. BIOCHEMICAL AND PHYSIOLOGICAL MECHANISMS IN GLUCOCORTICOID HORMONE INDUCTION OF MOUSE MAMMARY TUMOR VIRUS.

Scolnick EM, Young HA, Parks WP
National Cancer Inst., Bethesda, MD 20014
Virology; 69(1):148-156 1976

The mechanisms by which both constitutive and glucocorticoid-induced levels of mouse mammary tumor virus (MMTV) RNA can vary over 100-fold ranges were investigated in clones of cell lines (C3H MT) derived from mammary adenocarcinomas. MMTV-RNA increased 30-50% within 1 hr after addition of 5 ug/ml dexamethasone. This increase was inhibited by 5 ug/ml of actinomycin D, but not by cytosine arabinoside (5 ug/ml), hydroxyurea (10 ug/ml), or cycloheximide (100 ug/ml). It does not require new cellular protein or DNA synthesis. Increases in viral RNA precede increases in viral proteins. The identical kinetics of induction of RNA in the clone with low and high constitutive levels of MMTV-RNA suggested that the increases in MMTV-RNA may occur primarily via increases in the rate of synthesis of MMTV viral RNA.

108. RELATIONSHIP BETWEEN RECEPTOR AND MAMMARY TUMOUR VIRUS PRODUCTION AFTER STIMULATION BY GLUCOCORTICOID.

Shyamala G, Dickson C
Jewish General Hosp., 3755 Cote Ste-Catherine Road, Montreal, Quebec, Canada H3T 1E2
Nature (Lond); 262(5564):107-112 1976

The presence of cytoplasmic and nuclear glucocorticoid receptors in cultured primary mouse mammary tumor cells is reported, along with the accelerated production of mammary tumor virus (MTV) after 30 min exposure to glucocorticoids and the antagonistic action of progesterone. Binding studies of dexamethasone to receptors in cytoplasmic extracts indicated that saturation was reached at 4 x 10**-10 M, and Scatchard plots indicated a single class of binding site. The dissociation constant was estimated to be 1.6 x 10**-9 , and the number of binding sites per cell was estimated to be approximately 1,400. Binding activity was destroyed by treatment with pronase or trypsin, but not with DNase or RNase. The order of affinity of steroids for the receptor was dexamethasone greater than deoxycorticosterone greater than corticosterone greater than progesterone greater than hydrocortisone. Studies of the binding of dexamethasone to nuclear binding sites indicated that specific binding was complete by 30 min and saturation was reached with 10**-8 M dexamethasone. About 90% of the nuclear bound radioactivity could be solubilized, and the radioactivity was bound to a macromolecule. Pulsing the cell for 30 min was sufficient to evoke a subsequent near maximum stimulation of MTV. There was no evidence for type C virus production. Exposure of cells to progesterone alone (10**-4 - 10**-6 M) did not stimulate MTV but neither did it block the basal level of MTV production. At 10**-5 M progesterone, the stimulation of MTV production by 10**-6 M dexamethasone was inhibited by 10%, and at 10**-4 M progesterone, the inhibition was 70%. The failure of progesterone to remain bound to the receptor in the nucleus may be the reason that it cannot stimulate MTV, but its competition with dexamethasone for the cytoplasmic receptor accounts for its antagonism with dexamethasone.

109. GLUCOCORTICOID INDUCTION OF MURINE MAMMARY TUMOR VIRUS IN VITRO. (PP. 1151-1158)

Parks WP, Scolnick EM, Ransom JC
Tumor Viruses Cold Spring Harbor Symposia on Quantitative Biology; Cold Spring Harbor Lab. (Cold Spring Harbor, NY): vol. 39, 1975

Several cell lines developed from spontaneously occurring mammary adenocarcinomas were used to study the biological and biochemical parameters of murine mammary tumor virus (MMTV) in vitro. Immunoassays and determinations of the time course of MMTV synthesis and the inducibility of various MMT cell lines were performed after dexamethasone (1 ug/ml) treatment of the cells. In addition, the supernatant DNA polymerase activity, the dose-response of dexamethasone stimulation, and the ability of various hormones to induce MMT synthesis or interfere with dexamethasone stimulation of MMTV were measured. Addition of dexamethasone to a cell line increased supernatant polymerase activity significantly; it was first detected at 16 hr. Polymerase levels increased another 20 times over the next 72 hr, then declined slightly. The continued presence of dexamethasone was required for increased MMTV synthesis. Dexamethasone stimulation of murine cells proceeds through a highly specific mechanism to increase the levels of type B viral RNA transcription without increasing those of type C significantly. There was no evidence that dexamethasone treatment resulted in de novo transcription of MMTV from cells not already expressing constitutive amounts of MMTV gene sequences. The absolute levels of cytoplasmic receptor probably did not account for the biological patterns of MMTV induction. MMTV production was stimulated by dexamethasone in concentrations as low as 2.8 x 10**-10 M (physiologic levels). MMTV synthesis was also induced by hydrocortisone, corticosterone, and aldosterone, although these hormones were not as potent as dexamethasone. Progestins, estrogens, androgens, spermidine, insulin, and prolactin were ineffective as inducers, although testosterone, androstendione, progesterone, and 17a-hydroxyprogesterone were inhibitory. It appears that dexamethasone stimulation of MMTV synthesis proceeds via a highly specific allosteric interaction with a cytoplasmic receptor.

110. GLUCOCORTICOID-RECEPTOR INTERACTION AND INDUCTION OF MURINE MAMMARY TUMOR VIRUS.

Young HA, Scolnick EM, Parks WP
Natl. Cancer Inst., Bethesda, MD
J Biol Chem; 250(9):3337-3343 1975

The role of cytoplasmic receptors in the glucocorticoid induction of murine mammary tumor virus (MMTV) was analyzed in terms of specific binding and structure-activity relationships. S100 cytoplasmic extracts from the mouse mammary tumor cell line, C3H MT clone 6 were used for characterization of the glucocorticoid receptor. In the presence of varying concentrations of 3H-dexamethasone, saturation of the binding sites occurred at 4 x 10**-8 to 8 x 10**-8M with one class of receptor present. Dexamethasone , corticosterone and progesterone were comparatively effective in competing for hormone receptor. Dexamethasone (1 x 10**-10M) was the most potent induced of MMTV supernatant DNA polymerase. Negative results were obtained with progesterone and other steroids. Levels of nonradioactive hormone that blocked 3H-dexamethasone uptake in tissue culture closely paralleled levels necessary to inhibit cytoplasmic receptor binding. Cells which demonstrated markedly different MMTV phenotypic expression contained comparable levels of receptor. Increased amounts of dexamethasone-receptor complex were bound to nuclei with a plateau reached after 60 min of "activation." The major physiologic determinants of all these events appear to be hormone levels, receptor levels and transcription of the target cell chromatin.

111. REGULATION OF MOUSE MAMMARY TUMOR VIRUS GENE EXPRESSION.

Ringold GM
Univ. California, San Francisco, CA
Diss Abstr Int B; 37(5): 2078B 1976

The regulation of mouse mammary tumor virus (MMTV) gene expression was studied by measuring the production of virus and the transcription of viral genes in cultured cells. In cell lines and primary explants from mammary tumors of mice, the amount of virus produced correlated with the level of intercellular virus-specific RNA; this suggests that transcriptional controls are important in regulating the production of MMTV. The mechanism by which dexamethasone stimulates virus production was then investigated. The increase in virus production was a consequence of increased concentrations of intercellular viral RNA; this increase was dependent on RNA synthesis but not DNA synthesis. Further study indicated that the increase was due to both an increase in the rate of MMTV RNA synthesis and a decrease in its rate of degradation. The MMTV RNA was found to be preferentially associated with polyribosomes. (0 Refs)

112. INFLUENCE OF HIGH DOSE OF ESTRADIOL ON THE ICRC MOUSE BEARING TRANSPLANTED MAMMARY TUMORS.

Pai SR, Save PG

Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay

Indian J Med Res; 64(12):1788-1792 1976

The effects of estradiol on gonadectomized ICRC mice inoculated with transplanted mammary tumors or mammary tumor virus (MTV) obtained from acellular extracts of these mammary tumors were studied. The leukemoid reaction (splenomegaly and granulopoiesis) occurred in intact female syngeneic mice (24/50) and in syngeneic males (2/20) inoculated sc with a 10% mammary tumor homogenate containing intact tumor cells. The leukemoid reaction also was observed in 6/9 gonadectomized ICRC mice receiving mammary tumor cell homogenate and in 9/10 which received the mammary tumor cell homogenate accompanied by 10 ug estradiol. Lymphocytic leukemia developed in all groups treated with estradiol. Administration of 10 ug estradiol for 18 days induced lymphocytic leukemia in 1/10 gonadectomized ICRC mice treated with MTV-containing mammary tumor homogenates; 1/12 treated with MTV-containing acellular extracts; and 2/12 treated with estradiol alone. Immunological responses of gonadectomized mice receiving 9 or 18 injections of 10 ug estradiol daily showed that cellular and humoral immunity of the mice was unaffected. (26 Refs)

113. MOUSE MAMMARY TUMOR VIRUS AS A MODEL FOR VIRAL CARCINOGENESIS.

Gillette RW

Meloy Labs. Inc., 6715 Electronic Drive, Springfield, VA 22151

J Toxicol Environ Health; 1(4):545-550 1976

The interaction of mammary tumor virus (MTV), hormonal factors, and genetic background in murine mammary tumorigenesis is discussed. Mammary adenocarcinomas positive for the virus typically contain large numbers of type B particles. MTV-S of C3H mice and MTV-P of RIII mice have the highest oncogenicity. The tumors in RIII mice generally have the greatest response to hormone levels. They exhibit episodes of remission that depend on the physiologic status of the host. Requirements for prolactin, cortisone, and insulin have been demonstrated in vitro. About 95% of the females that reach third parity develop positive tumors, while virgin females produce about 20% tumors. The latency of tumors in MTV negative strains is much greater than in positive strains. In a study of expressions of MTV antigens in milk samples from hybrid mice of high and low expressor strains, high expressor strains produced significant amounts of virus at first parity, while low expressor strains only produced antigen after several pregnancies. MTV-positive mammary tumor induction is a good model for the study of viral oncogenesis; with the appropriate genetic background, 100% mammary tumors can be obtained if adequate hormonal components are provided.

114. HORMONE SYNERGISM IN THE IN VITRO PRODUCTION OF THE MOUSE MAMMARY TUMOR VIRUS.

Cardiff RD, Young LJ, Ashley RL

Dept. Pathology, Sch. Medicine, Univ. California, Davis, CA 95616

J Toxicol Environ Health; 1:117-129 1976

The hormone synergism in the production of the mouse mammary tumor virus in BALB/cfC3H mammary tumor cells is investigated by RNA-dependent DNA polymerase activity and radioimmune assay. When either estradiol, progesterone, prolactin, or thyroxin alone was added to the medium, a small but measurable effect was observed. The two-hormone combination of insulin and hydrocortisone increased virus production 8x, while the three-hormone combination of estradiol, insulin, and hydrocortisone increased production 20x. The peak production by four- and six-hormone combinations was transient, and further studies will have to be carried out to determine whether these combinations differ significantly from each other or from the three-hormone combination. It is concluded that hormones may act synergistically to stimulate virus production. (23 refs)

115. MOUSE MAMMARY TUMOR VIRUS PRODUCTION STIMULATED BY HORMONES AND POLYAMINES IN CELLS GROWN IN SEMI-SYNTHETIC IN VITRO CONDITIONS.

Svec J, Links J

Cancer Res. Inst., Bratislava, Czechoslovakia

Int J Cancer; 19(2):249-257 1977

Sykes' mouse mammary tumor cell line CCL-51, adapted to grow in semisynthetic medium, was studied to analyze the hormonal regulation of mouse mammary tumor virus (M-MTV) genome expression. Reverse transcriptase assay was used to quantitate the virus. The cells were found to produce detectable amounts of MMTV spontaneously in the absence of any hormones. Treatment with dexamethasone resulted in a hundredfold increase in MMTV production. MMTV production increased with time of exposure and with the number of subpassages. A combination of insulin and prolactin enhanced the stimulatory effect of dexamethasone, but insulin or prolactin alone had no effect on spontaneous MMTV synthesis. MMTV production was stimulated by spermidine but not by spermine or MgCl2. Pretreatment of the cells with 5-bromodeoxyuridine resulted in the suppression of dexamethasone-stimulated production. (29 Refs)

116. CELL CULTURE FACTORS INFLUENCING IN VITRO EXPRESSION OF MOUSE MAMMARY TUMOR VIRUS.

Fine DL, Arthur LO, Young LJ

RNA Virus Lab., NCI Frederick Cancer Res. Center, Box B, Frederick, MD 21701

In Vitro; 12(10):693-701 1976

The cell culture factors affecting the in vitro expression of mouse mammary tumor virus (MMTV) in the mouse adenocarcinoma cell line Mm5mt/C1 were assessed. Replicate flasks were seeded with densities of 1,3, or 5 x 10^4 Mm5mt/C1 cells per flask in the presence of DMEM-high glucose medium containing dexamethasone (DXM) and monitored over 10 days for the production of RNA-dependent DNA polymerase (RDDP). The other media evaluated were DMEM-low glucose, RPMI-1640, medium 199, L-15, and EMEM. Although a tenfold increase in RDDP activity was associated with DXM treatment for each seeding density, the greatest expression, either on a per-cell or per-milliliter basis, was achieved in cultures seeded at 5 x 10^4 cells per flask. No differences in time of max expression of MMTV antigens (day 6 post-DXM stimulation) were noted witn any of the media tested. However, max expression (percent cells positive for MMTV antigens) ranged from 70%-88%, with the highest values occurring in the EMEM-propagated cultures. Max expression of extracellular RDDP activity was observed 8 days post-DXM stimulation, and it varied with respect to the type of medium used. The highest activities were 490 and 910 picomoles/ml/hr/10^6 cells in RPMI-1640 and DMEM media, respectively. Between five- and tenfold higher RDDP activities were observed in DMEM-high glucose (4,500 mg glucose/liter) compared to DMEM-low glucose (1,000 mg/liter) cultures. Insulin alone had essentially no MMTV-RDDP stimulating activity. The presence of DXM resulted in a 10- to 30-fold increase in RDDP, depending on the medium used. Insulin in combination with DXM resulted in a 19- to

45-fold increase over the nontreated or insulin(alone)-treated cultures. The lack of cumulative RDDP activity at 37 C compared to 32 and 34 C suggested that MMTV activity could be unstable at 37 C. Incubation of Mm5mt/C1 cells at 37 C resulted in higher levels of virus production, as determined by virus particle count, antigen expression, and RDDP activity. However, a reduction in RDDP activity occurred concomitantly as a result of the thermoinstability of the virus and/or RDDP at the higher temperature. Virus expression in continuous mammary cell cultures is thus influenced by a variety of factors, including seeding density, culture medium, and incubation temperature. (30 Refs)

117. SUPPRESSION OF C-TYPE EXPRESSION IN LARGE-SCALE IN VITRO PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS (MEETING ABSTRACT).

Benton CV, Robinson OR, Schidlovsky G, Shibley GP
NCI Frederick Cancer Research Center, Frederick, Md 21701
Proc Am Assoc Cancer Res; 17():43 1976

Through the implementation of protocols designed to avoid certain physiological stress conditions, MuMTV production was accomplished in the virtual absence of endogenous C-type virus expression. Roller cultures of Mm5mt/cl cells derived from a C3H/Cgrl mammary tumor cell line (Owens and Hackett, 1972) produced C-type virus comprising 15-40% of total virus when propagated in a manner resulting in prolonged culture and, ultimately, monolayer retraction. C-type expression was detected by relative RNA-dependent DNA polymerase (RDDP) activity in the presence of B-type ($Mg^{2}+$) vs C-type ($Mn^{2}+$) cation specificities, immunodiffusion, polyacrylamide gel electrophoresis, complement fixation, electron microscopy and radioimmunoassay. By avoiding these conditions through the use of culture techniques that result in rapid proliferation of a sufficient quantity of Mm5mt/cl cells to produce large production lots (300-500 liters each) of virus released from dexamethasone treated cells, and by assaying cultures at each transfer level prior to production by immunodiffusion analysis of 1000-fold concentrates against MuRLV anti-p30 (sensitivity 0.5-1.0%), a product is obtained containing concentrate with 25-100,000 pM/ml/hr MuMTV-specific RDDP activity. Radioimmunoanalysis capable of detecting 2 ng MuRLV p30 proved negative for this material. (Author Abstract)

118. SURFACE LOCALIZATION OF VIRUS PRODUCTION ON A GLUCOCORTICOID-STIMULATED ONCORNAVIRUS-PRODUCING MOUSE MAMMARY TUMOR CELL LINE BY SCANNING ELECTRON MICROSCOPY.

Gonda MA, Arthur LO, Zeve VH, Fine DL, Nagashima K
Frederick Cancer Research Center (Litton Bionetics, Inc),Frederick, Maryland 21701
Cancer Res; 36(3):1084-1093 1976

A chronically infected continuous mouse mammary tumor cell line containing virus particles of type B morphology, free of contaminating type C virions, has been grown in tissue culture. These cells were treated with dexamethasone, a synthetic glucocorticoid, a potent stimulator of mouse mammary tumor virus expression. Surfaces of untreated and dexamethasone-treated cells were investigated by scanning electron microscopy. Untreated cells demonstrated a moderate expression of mouse mammary tumor virus (80 particles/cell) distributed diffusely over the cell surface. However, virions on dexamethasone-treated cells were localized in clusters of 100 to greater than 2000 virus particles, often with more than one cluster per cell. Dexamethasone-treated cells typically showed a 10-fold increase in cell-associated virus over untreated cells. Concentrated extracellular fluids from untreated and dexamethasone-treated cultures were quantitated for free virus. Dexamethasone-treated culture fluids demonstrated a similar 10-fold increase of extracellular particles, in contrast to untreated cultures. This increase in virus particles on the cell surfaces as well as in the extracellular fluids supports the theory that dexamethasone has a stimulatory effect on viral replication, not just on the release of budding particles. The ultrastruture of budding mouse mammary tumor virus during dexamethasone stimulation, determined by scanning and transmission electron microscopy, and the significance of such an in vitro system for viral immunodiagnosis are discussed.

119. MURINE MAMMARY TUMOR VIRUS: CHARACTERIZATION OF INFECTION OF NONMURINE CELLS.

Vaidya AB, Lasfargues EY, Heubel G, Lasfargues JC, Moore DH
Inst. Medical Res., Camden, NJ 08103
J Virol; 18(3):911-917 1976

Murine mammary tumor virus (MuTV) "proviral" DNA was detected in feline MuMTV infected feline and mink cells (CRFK-F2 kidney and CCL64 lung, respectively) by molecular hybridization using radioactive MuMTV complementary DNA as a probe. Kinetic analysis of MuMTV proviral DNA synthesis after infection showed that maximum MuMTV DNA synthesis was achieved by 8 hr; this was followed by a decline in detectable proviral DNA and eventual stabilization at a lower level. MuMTV synthesis in feline cells was greatly stimulated by the synthetic glucocorticoid, dexamethasone. On the other hand, MuMTV synthesis in mink cells was at a much higher level in the absence of dexamethasone, and the stimulation with dexamethasone was not as marked as in the feline cells. This difference in response may be due to different function and hormone dependence of the organs from which they were derived. Thermal denaturation of hybrids between MuMTV complementary DNA and infected mink cell RNA revealed no difference from homologous hybrids.

120. FACTORS INFLUENCING SYNTHESIS OF MOUSE MAMMARY TUMOR VIRUS BY CELLS GROWN IN CHEMICALLY-DEFINED MEDIUM.

Nagle SC
NCI Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21701
In Vitro; 12(4):316 1976

A chemically-defined, serum-free medium developed by Higuchi and Robinson was used by Bauer et al to grow a C3H mouse-derived cell (Mm5mt/cl) that allows replication of mouse mammary tumor virus (MMTV). This culture medium system has proved useful for studies on physiological requirements for virus synthesis and eliminates difficulties in data interpretation that may occur with other systems that do require serum for cell growth and/or virus replication. In these studies MMTV was measured as Mg11 dependent, RNA-dependent DNA polymerase activity in $pM/ml/hr/10^{3}$ cells. Dexamethasone, hydrocortisone, and insulin were all required for maximum virus synthesis. Glucose was required at a relatively high level (3600 mg/L) and omission of most individual amino acids resulted in reduced or no cell growth or virus synthesis. Ten high MMTV-producer clones of Mm5mt/cl continued to synthesize virus at high levels when subcultured in the defined medium for varying lengths of time. Studies on other factors tested in the defined medium, such as other hormones and cyclic AMP and dibutyryl cyclic AMP, will be discussed.

121. OPTIMIZATION OF DEXAMETHASONE-STIMULATED MM5MT/C1 CELLS FOR EXPRESSION AND RECOVERY OF MOUSE MAMMARY TUMOR VIRUS WITH HIGH RDDP ACTIVITY.

Brown BL, Orme LA, Bauer RF, Fine DL
NCI Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21701

In Vitro: 12(4):316 1976

In optimizing conditions for the in vitro production of mouse mammary tumor virus (MMTV), the C3H/C grl mouse adenocarcinoma cell line Mm5mt/c1 was grown in Dulbecco's modified essential medium containing 10**-5 M dexamethasone (DXM) and sampled at 6-hr intervals beginning day 3 post-seeding. Optimum viral Mg11 dependent, RNA-dependent DNA polymerase (RDDP) was released on the latter half of the 6th day and the beginning of the 7th day. RDDP activity ranged from 124 pM/ml/hr on day 3, to 13,666 pM/ml/hr on day 7. The cell growth peaks were maximum at 120, 138, and 162 hr, and cellular protein values were maximum at 120, 138, and 162 hr; whereas maximum RDDP activity was observed at 150, 162, and 174 hr, indicating that cell growth, protein synthesis, and viral RDDP expression may occur in cyclic phases. Virus production on a per cell basis was not influenced by initial cell inoculum size; however, temperature and concentration of DXM were contributing factors. Further results will be discussed.

122. VARIATIONS IN PHENOTYPIC EXPRESSION OF MMTV IN MOUSE MAMMARY TUMOR-DERIVED CELL CLONES.

Arthur LO, Fine DL, Plowman JK, Hillman EA
NCI Frederick Cancer Research Center, Frederick, Maryland 21701

Proc Am Assoc Cancer Res; 16:168 1975

A C3H/Cgrl mouse mammary tumor cell line (M-m5mt/c1) was cloned to derive subline(s) for producing large quantities of mouse mammary tumor virus with no or low murine leukemia virus expression and for providing cell lines for evaluating the viral enhancing effect of dexamethasone (DXM). Twenty-three clones, representing a cloning efficiency of approximately 30%, were isolated. The clones retained their epithelial-like morphology, but varied in MMTV expression from minimal to greater than the quantity of virus recovered from the parent line (monitored by exogenous RNA-dependent DNA polymerase (RDDP) assay, radioimmune precipitation and electron microscopy). Treatment with DXM (10**-5M) resulted in increased RDDP activity (2 to 35% increase over non-treated clones) and an $Mg^{2}+/Mn^{2}+$ ratio of 10 or greater in all clones. The high MMTV-producing clones, when inoculated into male and female C3H/He mice, induced tumors at the sites of inoculation within 2 weeks. These clones provide an in vitro source of MMTV, and a potential model for studying the genetics of MMTV expression as influenced by hormonal interactions. (Author Abstract)

123. EFFECT OF DEXAMETHASONE ON THE MOUSE MAMMARY TUMOR VIRUS GROWN IN CAT KIDNEY CELLS.

Lasfargues EY, Dion A, Lasfargues JC, Moore DH
Institute for Medical Research, Camden, N. J. 08103

Proc Am Assoc Cancer Res; 16:28 1975

A cell line, CRFK-F2, derived from the kidney cortex of a 10-week old kitten was infected by a murine mammary tumor virus (Lasfargues, et al, JNCI Dec 1974, in press). Infection has been repeated with freshly trypsinized CRFK-F2 cells treated in suspension with DEAE-Dextran (25 mu g/ml) then exposed to RIII virus. The MuMTV derived from skimmed RIII milk was purified by centrifugation on a sucrose density gradient. One month later, the cells grown in Eagle's MEM, 10% fetal calf serum and 10 mu g insuline per ml have shown a budding virus characterized as MuMTV by immunofluorescence and electron microscopy; it contained a reverse transcriptase whose activity was dependant on Mg ions. Addition of 10 mu g/ml of dexamethasone (DXM) to the culture medium produced a 6-fold increase of reverse transcriptase and a raise from 20 to 100% in the number of cells with a specific MuMTV membrane fluorescence. It is suggested that DXM might be effectively used for the detection of early stages of infection in mammalian cells exposed to that virus. (Author Abstract)

124. EFFECTS OF C-AMP AND DEXAMETHASONE ON MOUSE MAMMARY TUMOR VIRUS PRODUCING CELLS (MEETING ABSTRACT).

Plowman JK, Kelley SP, Fine DL
NCI Frederick Cancer Res. Ctr., Frederick, Md.

Proc Am Assoc Cancer Res; 15:104 1974

Recent observations by Sheppard (PNAS, 1971) and Johnson and Pastan (JNCI, 1972) have demonstrated modifications in cell morphology and growth with the treatment of transformed cells with cyclic-AMP. We have found that treatment of a mouse mammary tumor virus (M-MTV) containing cell line with dexamethasone (DXM) stimulates virus replication. As cyclic-AMP has been implicated as a 2nd messenger for DXM, studies were undertaken with dibutyl cyclic-AMP (dbC-AMP) to further investigate virus replication. Using cell membrane fluorescence (MIF) as an indicator of virus induced cellular antigen, dbC-AMP alone had no effect in increasing MIF. Dibutyl cyclic-AMP DXM treatment for 6 days produced higher % MIF than did cultures treated with DXM alone. However, after 8 days treatment % MIF in both test groups were both exceptionally high. Virus specific RNA-dependent DNA polymerase activity as measured using synthetic oligo dG poly rC template indicated high enzymatic activities in the treated cultures. These observations further delineate the mode of action of dexamethasone in enhancing MMTV replication.

125. ENHANCED PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS IN DEXAMETHASONE-TREATED, 5-IODODEOXYURIDINE-STIMULATED MAMMARY TUMOR CELL CULTURES.

Fine DL, Plowman JK, Kelley SP, Arthur LO, Hillman EA
NCI Frederick Cancer Res. Ctr., Md.

J Natl Cancer Inst; 52(6):1881-1886 1974

Medium containing 5-iododeoxyuridine (IUDR) (20 microg/ml) was added to cultures of C3H mouse-derived mammary tumor cells (Mm5mt) and left for 24 hours. An increase in virus-related RNA-dependent DNA polymerase (RDDP) activity was noted 7 days after IUDR treatment. In a second experiment, medium containing 40 microg/ml IUDR and varied concentrations of dexamethasone were added to Mm5mt cultures and left for 24 hours; the IUDR-containing medium was then replaced with medium containing dexamethasone at the appropriate concentration. When dexamethasone was present in the growth medium and in the medium after IUDR treatment, the levels of RDDP were increased. The greatest RDDP activity was obtained with 10**-5 M dexamethasone. Membrane immunofluorescence was also increased in the IUDR-treated cells, and further increased in the presence of dexamethasone. Membrane immunofluorescence enhancement was linear with the

concentration of dexamethasone. The number of B particles produced by the Mm5mt cells was also increased by IUDR and further increased by dexamethasone, as was the production of cell-associated mouse mammary tumor virus (M-MTV) antigens. These results further implicate hormones in MMTV replication and provide the basis for an in vitro MMTV production system.

126. DEXAMETHASONE STIMULATION OF MURINE MAMMARY TUMOR VIRUS EXPRESSION: A TISSUE CULTURE SOURCE OF VIRUS.

Parks WP, Scolnick EM, Kozikowski EH
Natl. Cancer Inst., Bethesda, Md.
Science; 184(1433):158-160 1974

In mouse cell lines derived from mammary adenocarcinomas the synthetic steroid dexamethasone stimulated production of murine mammary tumor virus. Viral RNA and antigens were increased as much as 20-fold over basal levels. In addition, a DNA polymerase similar to the type B viral reverse transcriptase was detected in culture fluid supernatants from a permanent cell line. Further results indicated that dexamethasone stimulation of MMTV antigen production in L8A C1 6 was accompanied by increases in MMTV RNA. These cells thus provide a possible tissue culture source of this virus and a model system for studying the mechanism of action of corticosteroids and the regulation of transcription of integrated viral DNA.

127. EFFECTS OF C-AMP AND DEXAMETHASONE ON MOUSE MAMMARY TUMOR VIRUS PRODUCING CELLS.

Plowman JK, Kelley SP, Fine DL
Frederick Cancer Res. Cent., NCI, Frederick, MD
Proc Am Assoc Cancer Res; 15:104 1974

128. CYCLIC AMP REGULATION OF MAMMARY TUMOR VIRUS PRODUCTION.

Yang J, Nandi S
Cancer Research Laboratory, Univ. of Calif., Berkeley, Calif. 94720.
Proc Am Assoc Cancer Res; 17:33 1976

Cell culture studies of mouse mammary tumors have shown that the regulation of MTV expression seems to involve, at least in part, insulin and cortisol. We now report that cyclic AMP may have an obligatory and a modulatory role on the stimulation of MTV production due to cortisol, as judged by measurement of MTV-specific reverse transcriptase activity from the media of cultured BALB/cfC3H mammary tumor cells. Its obligatory role is evident from the findings that under the conditions in which cortisol alone cannot stimulate MTV production, addition of dibutyryl cAMP or beta-adrenergic agonist isoproterenol can elicit stimulation. Its modulatory role is evident from the finding that under the condition in which cortisol alone can stimulate MTV production 5-10 fold, dibutyryl cAMP can further enhance the stimulation 2-3 fold. That the role of cyclic AMP in MTV production may be physiologically significant is suggested by two lines of evidence. The first indication is from the results which suggest that there appears to exist a correlation between cell density and cAMP amplification of MTV production due to cortisol. The second indication is derived from the presence of beta-agonist receptors on mammary tumor cells which respond to isoproterenol by increasing the intracellular level of cyclic AMP. (Author Abstract)

B. Hormonal Control of MuMTV Expression In Vivo

129. COMBINED EFFECTS OF 3-METHYLCHOLANTHRENE, MAMMARY TUMOR VIRUS, NODULE-INDUCING VIRUS, AND PROLONGED HORMONAL STIMULATION ON THE TUMOR-PRODUCING CAPABILITIES OF THE NODULE OUTGROWTH LINE D1.

Medina D, Faulkin LJ, DeOme KB
Baylor U. Coll. Med., Houston, Tex.
J Natl Cancer Inst; 44(1):159-15 1970

The incidence of mammary tumors from transplanted D1 hyperplastic alveolar nodules was enhanced from 8% (untreated controls) to 50% in BALB/c female mice, by admin of 3-methylcholanthrene (MCA; 1.0-3.0 mg/week po in divided doses), and further enhanced to 67% by the addition of prolonged hormonal stimulation from pituitary isografts. MCA did not significantly increase the incidence of mammary tumors in D1 nodule-bearing BALB/c f. C3H mice carrying mammary tumor virus (MTV), nor in MTV-carrying BALB/c f. C3H mice receiving prolonged hormonal stimulation. MCA stimulated tumorigenesis from the transplanted nodules in (C3Hf x BALB/c)F1 carrying nodule-inducing virus.

130. APPEARANCE OF VIRUS PARTICLES IN BALB/C MAMMARY NODULE OUTGROWTH LINES TRANSPLANTED INTO BALB/CF. C3H AND (C3HF X BALB/C)F1 MICE.

Medina D, DeOme KB, Pitelka DR, Colley VB
Dept. Zool., U. California Berkeley
J Natl Cancer Inst; 46(6):1153-1160 1971

Mammary nodule outgrowth cells from BALB/c mice were transplanted into a strain of mammary tumor virus (MTV)-harboring mice (BALB/cf C3H) and into a strain of nodule-inducing virus (NIV)-harboring mice (C3Hf x BALB/c)F1; in some cases recipient mice had undergone hormonal stimulation by means of pituitary isografts. The times at which MTV or the mammary nodule outgrowth cell lines (designated D1 and D2) were noted. Virus particles were found from 8-11 wk after transplantation in outgrowths transplanted into BALB/cf C3H mice; in hormone-stimulated mice of this strain, virus particles appeared at about the same time. Virus particles were not found in the outgrowths in (C3Hf x BALB/c) F1 mice until 44 wk after transplantation; when mice of this strain were stimulated by pituitary isografts prior to transplantation, virus particles appeared by 26 wk after transplantation. In a related experiment D1 outgrowths were transplanted into 21-wk-old mice and virus particles appeared 23 wk after transplantation; in mice which had been hormonally stimulated for 18 wk before transplantation, virus particles appeared within 13 wk after transplantation.

131. THE ROLE OF PROLACTIN IN CARCINOGENESIS. (PP. 107-136)

Kim U
Vitamins and Hormones, Advances in Research and Applications, Vol, 34. Munson PL, Glover J, Diczfalusy E, Olson RE, ed. New York, Academic Press, 1976.

The role of prolactin in carcinogenesis is described. Epidemiological studies of mammary cancer in different races suggest the existence of genetic differences in man, but they are often obscured by demographic differences. Some have postulated differences in estrogen or androgen metabolism, while others have presumed high risk factors because plasma prolactin is elevated in near relatives of breast cancer patients. The susceptibility of mice to mammary tumor virus is highest at birth and during the nursing period and decreases with age.

High dietary fat increases mammary tumor incidence in rats given chemical carcinogens. This has been attributed to elevated serum prolactin levels. Under estrogenic stimulation, the mammotropes promptly undergo hyperplasia, with increased secretion of prolactin. This is a reversible process. Regression of hypersecretion of prolactin follows cessation of estrogenic stimulation. However, if the estrogenic stimulation is uninterrupted, some prolactin cells can undergo neoplastic transformation followed by formation of prolactin-secreting adenomas. The discovery of the hypothalamic hormones and agents acting by way of the hypothalamus has emphasized the role of prolactin in mammary carcinogenesis. The triggering mechanism of mammary tumorigenesis can lie in the CNS. Prolactin appears to be the key hormone, although estrogens also are frequently involved. Prolactin acts on the plasma membrane of the mammary gland, where its instructions for growth and function of the mammary epithelium are carried out by cyclic AMP. The fact that mammary tumors cannot be induced in hypophysectomized animals in the absence of prolactin calls for reconsideration of the view that the major direct mammary carcinogens are ovarian steroids. (233 Refs)

132. UTERINE, VAGINAL, AND PROLACTIN RESPONSES TO DIETARY DIETHYLSTILBESTROL IN THE MOUSE. (MEETING ABSTRACT).

Greenman DL, Cernosek SF, Gutierrez-Cernosek RM
Natl Ctr Tox Res, Jefferson, AR 72079
Fed Proc; 36(3):912 1977

Vaginal, uterine, and prolactin responses to diethylstilbestrol (DES) were examined in three strains of mice: C3H/HeN-MTV**+, C3H/HeN-MTV**-, and C57Bl/6JNctr x BALB/c ST Crl Nctr (hybrid). Mice were fed a diet containing graded concentrations of DES for 6 days prior to sacrifice. Vaginal smears showed no apparent differences in response to DES for the three strains. Virtually all mice exhibited a positive response at greater than or equal to 80 ppb. Uterine weights of mice ingesting 0-500 ppb of DES showed 1) no differences in response between MTV**+ and MTV**- mice with a maximal uterine weight response of approx 40 mg at 80 ppb, and 2) a wider dose response to DES in the hybrid mice with a maximal uterine weight of approx 70 mg at 250-500 ppb. Purified mouse prolactin supplied by Dr U Lewis (Scripps Inst, La Jolla, CA) was used to develop a radioimmunoassay in our laboratory. Both MTV**+ and MTV**- mice had 3-6 fold higher serum prolactin levels at greater than or equal to 160 ppb of ingested DES doses as compared with their respective control values. Serum prolactin levels from the hybrids increased significantly (2.5 fold higher) when DES doses of greater than or equal to 20 ppb were ingested. Thus, it appeared that in these mouse strains the three end-points examined may give different dose response curves. (Author Abstract)

133. MAMMARY TUMORIGENESIS AND PATHOLOGIC CHANGES OF THE REPRODUCTIVE TRACT OF FEMALE MICE CONTINUOUSLY FED DIETHYLSTILBESTROL AND 17BETA-ESTRADIOL FOR 18 MONTHS (MEETING ABSTRACT).

Norvell MJ, Farmer JH, Highman B, Shellenberger TE
NCTR, Jefferson, AR.
Proc Am Assoc Cancer Res; 18:243 1977

To obtain a dose response curve to mammary tumorigenesis and to study the long-term effects of estrogen administration on the reproductive tract, virgin female C3H/HeJ mice are being fed graded levels (10, 100, 500 mug/kg) of diethylstilbestrol (DES) and 17beta-estradiol (100, 1000, 5000 mug/kg) continuously from six to 104 weeks of age. A comparable population of C3HeB/FeJ mice are being fed DES at 10, 100, and 500 mug/kg. Mammary tumors produced during the first 78 weeks of the study showed a dose response relationship to DES and 17beta-estradiol in the C3H/HeJ mice but not to DES in the C3HeB/FeJ mice. Estrogen induced pathologic changes observed at the 78 week serial sacrifice included adenosis of the cervix, hyperplasia of the glands of the uterus, atrophic ovaries and uterine adenocarcinomas. These findings indicate that the mammary tumor virus factor promotes DES or estradiol induced mammary tumorigenesis in C3H mice, but that other DES and estradiol induced carcinogenic and precarcinogenic lesions of the reproductive tract are independent of the MTV. (Author Abstract)

134. CARCINOGENIC EFFECTS OF ORAL DIETHYLSTILBESTROL ON C3H MALE MICE WITH AND WITHOUT THE MAMMARY TUMOR VIRUS.

Gass GH, Brown J, Okey AB
Physiol. Dept., Southern Illinois Univ., Carbondale
J Natl Cancer Inst; 53(5):1369-1370 1974

Prolonged oral diethylstibestrol (DES) exposure and the presence of mouse mammary tumor virus (MMTV) in eventual mammary tumor formation was studied in castrated C3H/An male mice (with the mammary tumor virus) and C3H/Anf castrated male mice (presumably free of the virus). Mice of both substrains were observed for mammary tumor formation during 18 months on either DES-containing (at 250 ppb) or control (DES-free) diets, while others were observed for 12 months. In groups on control diets, no mammary tumors were found in 80 C3H/An mice, and only one tumor was found in 80 C3H/Anf mice. In groups receiving DES, tumor incidence was 45/80 for C3H/An and 5/80 for C3H/Anf mice. The results showed that oral intake of DES was highly carcinogenic in genetically susceptible, MMTV-bearing mice but has little or no carcinogenic activity in MMTV-free mice of the same strain, even when administered continuously for as long as 18 months. The mechanism of interaction between the hormone and virus in tumor initiation/promotion in unknown.

135. LONG-TERM EFFECTS OF NEONATAL STEROID EXPOSURE ON MAMMARY GLAND DEVELOPMENT AND TUMORIGENESIS IN MICE.

Mori T, Bern HA, Mills KT, Young PN
Department of Zoology and Cancer Research Laboratory, University of California, Berkeley, CA 94720.
J Natl Cancer Inst; 57(5):1057-1062 1976

Newborn female mice of three strains-BALB/cfC3H (mammary tumor virus (MuMTV)-infected), BALB/c, and C57BL (both virus-free)-were given injections of 17beta-estradiol or testosterone, alone or in combination with ovine prolactin, for the first 5 days of life. Half of each group of mice were ovariectomized at 40 days of age, and all mice were killed between 6 and 16 months of age. Mammary glands of BALB/cfC3H mice receiving steroid hormones were better developed than those of mice not receiving steroids. Androgen induced a higher incidence of grossly dilated ducts and secretion-filled alveoli. Mammary nodule and tumor incidences were higher in steroid-treated mice than in controls; androgen resulted in higher incidences than did estrogen. The age of onset of mammary tumors was also earlier after neonatal steroid treatment. In BALB/c mice, neonatal injections of estrogen induced some alveolar development of the mammary gland; neonatal injections of ovine prolactin had a greater effect. The mammary glands of C57BL mice did not show any evidence of stimulation by neonatal hormone treatment, which indicated the probability of strain differences. However, no nodules or tumors occurred in these MuMTV-free strains. Therefore, MuMTV was essential for neoplastic mammary responses to neonatal hormone treatment. Ovariectomy prevented alveolar development and abnormal changes in the mammary glands of all groups, thus

indicating that ovary-independent alterations in the mammary gland were not induced by neonatal steroid treatment. We concluded that neonatal steroid exposure resulted in increased mammary tumor risk in mice, but only in the presence of both MuMTV and ovaries. (Author Abstract)

136. NODULE BIOASSAY OF THE MOUSE MAMMARY TUMOR VIRUS: MODIFICATIONS AND QUANTITATIVE CONSIDERATIONS.

Nandi S, Haslam S, Helmich C, Ritter RI
Dept. Zool., U. California, Berkeley
J Natl Cancer Inst; 46(6):1309-1315 1971

Extracts of mammary tissues from mammary tumor virus (M-MTV)-infected mice (strains C3H, DBA/2 and BALB/cfC3H) were injected in varying concentrations into uninfected mice; recipients were given implanted pellets of estradiol plus deoxycorticosterone 4 wk after inoculation with M-MTV. The development of mammary hyperplastic nodules in hormone-treated virus-infected recipients was observed in connection with a standard bioassay of M-MTV in infected mice. The overall mortality of hormone- and virus-treated mice ranged from 20-50%. All dilutions of mammary tissue from M-MTV-infected donors produced nodules in recipients; dilutions of 10-2 to 10-5 or 10-6 resulted in no evident decrease in biologic activity. Beyond this point further dilutions resulted in a gradual or precipitous decrease in nodule incidence. In a related experiment recipient mice were inoculated with whole blood or with red blood cells from mice infected with the blood-borne variety of M-MTV (R-MTV); 1 wk after virus inoculation, recipients were given 2 pituitary isografts. Isografts were destroyed by electrocauterization 9 wk later and the incidence of mammary hyperplastic alveolar nodules was observed. MTV activity was detected in mice receiving infective red blood cells at dose levels between 10-1 g equivalent (109 cells) and 10-3 or 10-4 equivalent (106 or 107 cells). Mice receiving R-MTV-infected blood were given 1,2 or 3 pituitary isografts under the kidney capsule in an attempt to reduce the mortality among test mice during the assay period. Mortality among mice used in the R-MTV assay and given 1-3 pituitary isografts was less than 2%. Nodule assay with pituitary isografts also reduced the time elapsed between infection with virus and appearance of nodules.

137. MODIFYING EFFECTS OF A BENIGN VIRUS ON THE MALIGNANT PROCESS AND THE ROLE OF PHYSIOLOGICAL STRESS ON TUMOR INCIDENCE. (pp. 319-336)

Riley V, Spackman D
Modulation of Host Immune Resistance in the Prevention or Treatment of Induced Neoplasias. NCI and John E, Fogarty International Center for Advanced Study in the Health Sciences, Bethesda, MD, 1977.

The ip administration of lactate dehydrogenase (LDH) virus, which is a benign passenger in most classical transplantable mouse tumors and oncogenic virus preparations, elevated corticosterone levels significantly in three strains of 6-to 10-wk-old female mice. These elevations apparently caused thymus involution and lymphocytopenia. When LDH virus was administered together with oncogenic viruses, tumor growth was significantly enhanced, presumably because of a decrease in cell-mediated immunity. In genetically susceptible C3H/HeJ female mice carrying the Bittner mammary tumor virus from birth, tumor incidence was dramatically reduced from about 90% in mice housed under sustained stress to less than 10% in mice housed in plastic cages held in specially designed protective, enclosed, ventilated shelves that minimize stress induction. The data suggest that social and physiological stress may compromise immunological competence and thus enhance malignancy. Reexamination of earlier experimental data on tumor induction in mice is recommended. (102 Refs)

138. OF STRESS, VITAMIN A, AND TUMORS.

Seifter E
Dept. Biochemistry, Albert Einstein Coll. Medicine, Yeshiva Univ., Bronx, NY 10461
Science; 193(4247):74-75 1976

The increase in tumor incidence in mice infected with mammary tumor virus as a result of exposure to environmental stresses may be due to depression of cell-mediated immune reactions caused by the hypersecretion of corticosterone. The author presents data that support this hypothesis: mice inoculated with a murine sarcoma virus (MuSV-M) have increased incidences and severity of tumor development when exposed to physical stress. Metyrapone, a drug that inhibits corticosterone production, prevents the typical stress reaction and increases the resistance of stressed and nonstressed mice to MuSV-M. Steroids, which can compete with corticosterone, and vitamin A, which blocks some host responses to stress, are also protective against both thymic involution and tumor development following inoculation with MuSV-M. Vitamin A inhibits the growth of C3HBA transplanted tumor cells. (8 refs)

139. MOUSE MAMMARY TUMORS: ALTERATION OF INCIDENCE AS APPARENT FUNCTION OF STRESS.

Riley V
Dept. of Microbiology, Pacific Northwest Res. Foundation, and Fred Hutchinson Cancer Res. Center, Seattle, WA 98104
Science; 189(4201):465-467 1975

The effect of different experimental and environmental conditions on mammary tumor incidence and latency was studied in C3H/He mice carrying the Bittner strain of mammary tumor virus. From 80-100% of these mice usually develop mammary tumors within 8-18 mo after birth when studied under the usual housing and experimental conditions. Four groups of mice were investigated: parous mice housed under conditions of chronic environmental and manipulative stress (group A); nonparous mice housed under the same conditions of chronic environmental and manipulative stress (group B); nonparous mice housed under protective conditions and subjected to moderate intermittent stress (group C); and mice provided with maximum protection from environmental and manipulative stress (group D). The last group was a combination of parous, nonparous, and virgin mice delivered by cesarean section and foster-nursed to deplete the milk-passaged tumor virus. The median tumor latency period for group A was 276 days compared with 358 days for group B. In group C the median latency period was 566 days, a significant extension over both groups A and B. At 400 days of age, the incidence of spontaneous mammary tumors was 92% in group A, 60% in group B, and 7% in group C. Group D had no such small tumor incidence that determination of a median latency period was not possible. At 21 mo of age, one mammary tumor was detected in 75 surviving mice. The data suggest that moderate chronic or intermittent stress may predispose C3H/He mice to an increased risk of mammary carcinoma, possibly through a resultant compromise of their immunological competence or tumor surveillance system, and that adequate protection from physiological stress may reduce the occurrence of the mammary tumors.

140. THE ROLE OF PHYSIOLOGICAL STRESS ON BREAST TUMOR INCIDENCE IN MICE.

Riley V, Spackman D, Santisteban G
Pacific Northwest Research Foundation, The Fred Hutchinson Cancer Research Center, and Seattle University, Seattle, Washington 98104
Proc Am Assoc Cancer Res; 16:152 1975

Presumed identical groups of C3H/HeJ female mice carrying the mammary tumor virus have been monitored for mammary tumor incidence while housed and handled under two different conditions in respect to exposure to chronic stress. Conventional open-rack facilities were employed for the stressed mice, whereas specially designed, protective facilities were used to minimize disquieting noises and odors, temperature fluctuations, infections, and other stress-inducing factors. Although all of the mice studied were potential candidates for virus-induced breast malignancy, the mice protected from stress exhibited only 7% tumor incidence at 12 months as compared with 92% tumors in those mice maintained under conventional stress-associated conditions. Mouse stress is expressed biochemically by an increase in plasma corticosterone which is thus used in our laboratory for detecting and quantitating stress status. Closely correlated with the elevation of this hormone is a significant decrease in circulating T-cells and an involution of the thymus. A tentative hypothesis for guidance in the further examination of these phenomena assumes that the biochemical and cellular consequences of physiological stress have adverse influences on the host surveillance systems, which thus permit a newly transformed cancer cell a greater opportunity to survive and to establish itself as a viable, irreversible neoplasm. (Author Abstract)

141. BIOACTIVITY OF C3H AND RIII MAMMARY TUMOR VIRUSES IN VIRGIN FEMALE BALB/C MICE: BRIEF COMMUNICATION.

Squartini F, Bistocchi M
Inst of Pathological Anatomy and Histology, Medical Sch, Univ of Pisa, Via Roma 57, 56100 Pisa, Italy
J Natl Cancer Inst; 58(6):1845-1847 1977

The bioactivities of C3H and RIII mammary tumor virus (MuMTV) in virgin female BALB/c mice differed. The average number of mammary hyperplastic alveolar nodules per mouse after noduligenic tests was 20.1 in BALB/cfC3H and 10.7 in BALB/cfRIII females. Spontaneous mammary tumor incidence after 20 months of observation was 47.5% in BALB/cfC3H and 14.6% in BALB/cfRIII females (P less than 0.01). The frequency of lung metastases in mammary tumor-bearing mice was 63.1% in BALB/cfC3H and 16.6% in BALB/cfRIII females (P less than 0.05), although the clinical duration of mammary tumors was the same. These data demonstrated a lower bioactivity of RIII MuMTV when compared to C3H MuMTV in BALB/c mice and suggested that the causative virus may control all the steps of mouse mammary tumor development, including metastasis. (22 Refs) (Author Abstract)

142. RESPONSE OF C3H-AVYFB FEMALE MICE TO A LOW ONCOGENIC, MILK-BORNE MAMMARY TUMOR VIRUS.

Vlahakis G
Natl. Cancer Inst., Bethesda, Md. 20014
J Natl Cancer Inst; 55(5):1217-1218 1975

On testing a low oncogenic milk-borne mammary tumor virus (MTV) of strain DD in C3H-AvyfB mice, as compared with the similar strain C3HfB, mammary tumors were observed to occur with a higher incidence and at lower age in C3H-AvyfBfDD (with DD-MTV) than in C3HfBfDD (with DD-MTV), in virgin females. Since the effect of breeding tended to mask any difference between the breeders, mammary tumor incidences were similar (with a slightly higher age at tumor occurrence in the C3H-AvyfBfDD females). Therefore, the C3H-AvyfB virgins (with the Avy gene) were almost as susceptible to mammary tumors with the less potent DD-MTV as were C3HfB virgins with the more virulent C3H-MTV of strain C3H.

143. OCCURRENCE AND PRENEOPLASTIC SIGNIFICANCE OF HYPERPLASTIC ALVEOLAR NODULES (HAN) IN THE STRAIN GR MOUSE.

Miyamoto MJ
Cancer Res. Laboratory and Department of Zoology, University of California, Berkeley, California 94720
Proc Am Assoc Cancer Res; 17:33 1976

GR (MTV+) mice develop 2 types of mammary tumors: pregnancy dependent tumors (PDT) that develop only during pregnancy and regress within a few days after parturition and, independent mammary tumors (IMT). IMT develop in both parous and virgin GR mice, and their progressive growth is not influenced by pregnancy or ovariectomy. HANs are also found in GR mammary glands. HANs have been shown to be preneoplastic in other MTV+ mouse strains. Studies on 6 different GR HAN outgrowth lines have now shown that GR HAN are also preneoplastic. The tumors developing within these HAN transplants were IMTs. PDTs did not develop within HAN outgrowths during pregnancy. Outgrowths resulting from the injection of single cell suspensions of normal GR mammary cells into the gland-free fat pads of virgin GR mice frequently contain lobulo-alveolar (LA) areas. Transplantation studies and tumor tests have shown that this LA is equivalent to tissue-transplant-derived HAN outgrowths. These studies with dissociated normal mammary glands show that cells with HAN potential are present in GR mice as young as 2 months. Preliminary results from similar studies on dissociated PDTs indicate that cells with HAN and IMT potential are also present in these tumors. (Author Abstract)

144. PATHOLOGY OF SOLID TUMOURS IN MICE.

Dux A
Netherlands Cancer Inst., Amsterdam, The Netherlands
Int Union Cancer Tech Rep Ser; 20:36-39 1975

The incidence and histology of solid tumors in inbred strains of mice are reviewed. The most common solid tumors in inbred mice are mammary tumors in breeding females, lung tumors, and hepatomas. The incidence of these tumors is different in the various strains but no strain is absolutely refractory to the development of tumors. Genetic factors determine a graded susceptibility for the development of tumors. There is no parallelism in the frequencies: a strain with a high incidence of one tumor may have low frequencies of others. Mammary tumors are the most frequent in the strains studied; they may be classified into five groups: adenocarcinoma type A, B, and C, adenoacanthoma, and carcino-sarcoma. Most mammary tumors developing at an early age in females injected with the mammary tumor virus are adenocarcinomas type A or B. Type C adenocarcinoma and adenoacanthomas occur mostly in very old females. Two other types of mammary tumor have also been reported: pale cell carcinoma, which is observed in virgins and hormone-treated mice of the GR strain, and type P (pregnancy-dependent) tumors, which are characterized by an organoid structure. In mice, pulmonary tumors are alveogenic and are variously diagnosed as adenoma, papillary cystadenoma, and adenocarcinoma. They are rounded, pearly-white nodules, often just under the pleura. In the mouse, hepatomas are usually round masses on the surface of the lobes, sometimes pedunculated. In addition to these three common types of malignant tumors, a great variety of tumors can be observed in

all organs and tissues of the mouse, although without experimental manipulation the incidence of these tumors in mice is very small.

145. PREGNANCY DEPENDENCE OF MAMMARY TUMORS IN STRAIN DDD MICE.

Matsuzawa A, Yamamoto T, Suzuki K
Inst. Med. Sch., Univ. Tokyo, Japan
J Natl Cancer Inst; 52(2):449-454 1974

Twenty-two mammary tumors from retired breeder DDD mice aged approximately 12 months were transplanted into virgin mice, half of which were force-bred so that the tumors could be examined for pregnancy-dependence. The influence of pregnancy on tumor growth was determined by comparing graft-take rate, latent period, final tumor weight and growth curves between virgin and breeding groups. Four tumors were classified as completely pregnancy-dependent (CPF), two as moderately pregnancy-dependent (MPD), three as slightly pregnancy-dependent (SPD) and 13 as pregnancy-independent (PID). The CPD tumors did not grow in virgins but grew rapidly in pregnant breeders and regressed after parturition, reaching ascending peaks in successive pregnancies. Morphologically, all CPD tumors were type A; composed of glandular spaces of various sizes surrounded by a single layer of small, cuboidal epithelial cells and filled with a milky secretion. One MPD tumor was a pale-cell carcinoma. Two of the SPD tumors were type A + B and the third, type P. PID tumors consisted of three type A + B tumors without secretory activity, five type P, three pale-cell carcinomas and two mixed tumors. These findings suggest that the mammary tumor virus of strain DDD may belong to a plaque-inducing mammary tumor virus.

146. STUDIES ON DDD MOUSE WITH SPECIAL REFERENCE TO MAMMARY GLAND TUMORS.

Matsuzawa A, Yamamoto T, Suzuki K
Inst. Med. Sci. U. Tokyo, Japan
Jpn J Exp Med; 40(3):159-181 1970

The incidence of mammary tumors in virgin mice of the DDD strain, the association of viruses with these tumors, and the tumor-bearing status of pregnant and multiparous mice were studied together with other factors implicated in mammary tumorigenesis. Mammary tumors reached maximum development in virgin mice at the age of 6 months, and atrophic changes in these tumors coincided with decreases in the hormone-producing components of the ovaries. Mammary hyperplastic nodules (averaging 2 in number) were found in virgins above 9 months of age with nodules becoming abundant by 15 months. Hyperplastic nodules could be induced by hormonal stimulation (estrogen + deoxycorticoacetate) in 5-wk-old mice. Mammary plaques were rare; however, the mice were found to harbor mammary tumor virus and to transmit it to offspring via breast milk. Mammary tumors and neoplasms of reticular tissue occurred at a mean age of 16.4 months in 34.4% of 67 virgin mice. In 2 force-bred strains mammary tumors developed at an incidence of 71.5 and 90%. Mammary tumor virus appeared to be weakly oncogenic in DDD strain mice but strongly oncogenic in strain BALB/cJms mice. All mammary tumors developed were adenocarcinomas.

147. PRESENCE OF A, B, AND C VIRUSLIKE PARTICLES IN ORGANS OF RIII/DM/SE MICE.

Bucciarelli E, Bolis GB, Squartini F
Dept. Res. Cancer, U. Perugia, Italy
Lav Ist Anat Istol Patol (Perugia); 30(2):57-72 1970

Electron microscopic investigations of the distribution of viral particles were made in various organs (mammary gland, epididymis, spleen, thymus, bone marrow and lymph nodes) of RIII/Dm/Se female and male mice in the following conditions: one 15-month-old virgin female; two 8-month-old lactating females (3rd pregnancy); 7 multiparous females; one 14-month-old leukemic female; and 6 normal males (8-15 month-old). Four types of viral particles were observed: intracisternal A-type particles, C-type particles (leukemic virus), cytoplasmic A-type particles and B-type particles (MTV). The intracisternal A-type particles were present in most of the organs of normal male, normal and leukemic or mammary gland tumor-bearing female mice; larger amounts were found in the thymus, spleen, marrow and lymph nodes of normal males and leukemic females. C-type particles occurred frequently but never in large amounts in the thymus, spleen and lymph nodes of the leukemic virgin female, the normal males, and the tumor-bearing females as well as in the nipples of lactating females. The cytoplasmic A-type particles were found in the lactating nipples, the mammary gland tumors and the epididymal tissues and were constantly associated with B-type particles in the epithelial cells of these tissues. The presence of cytoplasmic A particles in the thymus, spleen and lymph nodes suggested a possible direct replication of MTV in the lymphopoietic organs; this hypothesis was supported by the bud-like accumulations of these particles in the spleen and lymph nodes of mammary gland tumor-bearing animals, resembling the early stages of development of the B particles.

148. TWO-WAY SELECTION OF A STOCK OF SWISS ALBINO MICE FOR MAMMARY TUMORIGENESIS: ESTABLISHMENT OF TWO NEW STRAINS (SHN AND SLN).

Nagasawa H, Yanai R, Taniguchi H, Tokuzen R, Nakahara W
National Cancer Center Research Institute, Tsukiji 5-1-1, Chuoku, Tokyo 104, Japan.
J Natl Cancer Inst; 57(2):425-430 1976

Two mouse strains (SHN and SLN) with high and low incidences, respectively, of mammary tumors were established from the same basal stock of Swiss albino mice that were unrelated in origin to other mouse strains with mammary tumors. In the breeders, mammary tumor incidence and average age of the mice when they developed mammary tumors were 97.2% and 6.6 months for SHN, and 55.7% and 10.1 months for SLN, respectively. In virgins, tumor incidence and age at development of tumors were 88.3% and 8.7 months for SHN, and 9.7% and 14.4 months for SLN, respectively. In SLN mice, the efficiency of selection was more marked in virgins than in breeders. The number of mammary tumors per mouse was significantly higher in SHN than in SLN. SHN females were superior to SLN females in normal and preneoplastic mammary growth, reproductivity, lactation performance, mammary sensitivity to pituitary mammotropin, and activity of mammary tumor virus. Selection had little effect on the pituitary prolactin secretion. (Author Abstract)

149. MAMMARY GLAND TUMORS IN SUBSTRAINS C57BL/M AND C57BL/HE MICE.

Heston WE, Vlahakis G, Smith GH
Natl. Cancer Inst., Bethesda, Md.
J Natl Cancer Inst; 49(3):805-812 1972

A few spontaneous mammary tumors were observed in breeding female mice of substrains C57BL/M and C57BL/He; the incidence of C57BL/M was somewhat higher than in C57BL/He. This correlates with former observations that whereas C57BL/He is genetically resistant to the mammary tumor virus (MTV), C57BL/M is much more susceptible. Mammary tumors were induced with hypophyseal isografts without the introduction of MTV in both substrains and, as further correlation with their genetic susceptibility, the incidence in the C57BL/M females was somewhat higher than in the C57BL/He females. All the hypophyseal isograft-

stimulated mammary tumors were adenoacanthomas. No morphologic evidence was obtained for the presence of "derepressed" MTV in these C57BL mammary tumors induced by hypophyseal isografts. In the primary spontaneous tumors extracellular particles and budding forms were observed. Some of these were classified as type-C particles but others were difficult to interpret. The possibility that some of these particles were type B remains open. In line with the genetic resistance and susceptibility of the two substrains, these extracellular particles were seen only in the spontaneous tumors of the C57BL/M substrain. The spontaneous tumors were intertransplantable between the two substrains, though the substrains have been separated since before 1936.

150. VIRUSES IN OSTEOSARCOMAS INDUCED BY 226RA: A STUDY OF THE INDUCTION OF BONE TUMOURS IN MICE.

Lloyd EL, Loutit JF, Mackevicius F
Radiological and Environmental Res. Div., Argonne Natl. Lab., Argonne, Ill. 60439
Int J Radiat Biol; 28(1):13-33 1975

Experiments were carried out to determine if a virus is involved in the production of bone tumors, if sex affects the incidence of bone tumors, and if one strain of mice is more likely to develop osteosarcoma. Male C3H/H mice, female C3H/H mice, and female CBA/H mice, divided into three groups of 15 animals each, were injected ip with 0.5 microCi 226Ra (a dose previously shown to be associated with a high incidence of osteosarcoma). Osteosarcomas developed in 14 of the female C3H/H mice (animals known to carry mammary tumor viruses in milk), but in only six of their 15 male counterparts. Among uninjected C3H/H controls, only one male and no females developed osteosarcoma. Mammary tumors occurred in nine of the experimental females and in ten of the control females. In the CBA/H mice, which have a very low incidence of mammary tumors and leukemia, seven of the 15 injected females developed osteosarcoma. No osteosarcomas were observed in the controls, and no mammary tumors occurred in either the injected or control groups. The CBA/H mice lived about 5-8 mo longer than C3H/H mice, and their osteosarcomas appeared at a correspondingly later date. Virus particles were detected in each of the three mammary tumors and in 15 of the 17 osteosarcomas examined by electron microscopy. It cannot be concluded that osteosarcomas are caused by a virus; however, the results suggest that viruses may at least contribute to the development of osteosarcomas in mice.

C. Other Factors Affecting MuMTV Expression

151. HIGH FREQUENCY VARIATION IN MAMMARY TUMOR VIRUS EXPRESSION IN CELL CULTURE.

Parks WP, Hubbell ES, Goldberg RJ, O'Neill FJ, Scolnick EM
Laboratory of Tumor Virus Genetics National Cancer Institute, Bethesda, Maryland 20014
Cell (Camb); 8(1):87-93 1976

Clonal derivatives of C3HMT murine mammary cell lines in culture demonstrate conversion of mammary tumor virus (MMTV) expression at a rate of approximately 6 per 100 clones. This alteration is largely unidirectional from a relatively high level (MMTV**H) to a 10 fold lower level (MMTV**L). This high rate of MMTV**L variant conversion is in apparent contrast to the presumably mutational rate (approximately equal to 3 per million cells) that governs development of resistance to 6-thioguanine (TG) in the same mammary cells. In somatic cell hybrids between different MMTV TG**r clones and mouse or hamster TK- cells, expression of constitutive levels of MMTV and responsiveness to dexamethasone induction is dominant. Thus MMTV expression is regulated by at least two levels of positive control, constitutive expression and glucocorticoid stimulation, but the former is subject to a high rate of variant formation. (Author Abstract)

152. BIOLOGICAL ACTIVITIES OF MURINE MAMMARY TUMOUR VIRUS IN VITRO. INCREASED MACROMOLECULAR SYNTHESES IN MOUSE AND HAMSTER KIDNEY CELLS; PRODUCTION OF B- AND C-PARTICLES IN THE MOUSE CELLS.

Links J, Tol O, Calafat J, Buijs F
Div. Virology, Netherlands Cancer Inst., Sarphatistraat 108, Amsterdam, Netherlands
Eur J Cancer; 13(6):539-548 1977

Murine mammary tumor virus (MTV) induced an increased net synthesis of DNA, RNA and protein in short-term cultures of baby mouse kidney cells (BMKC) made from two different BALB/c mouse substrains (He A and Crgl A). The dose-response ratio went through a max but growth inhibition was not observed. Similar effects were induced in baby hamster kidney cells (BHK21/C 13). In longer-term cultures of MTV-infected BMKC, foci of piled-up small rounded epithelioid cells appeared on the monolayers. Cell lines derived from these foci grew well in media without serum and produced biologically active MTV (B-particles) and murine leukemia virus (MLV; C-particles). Higher in vitro passages of these cell lines induced less early (less than 300 days) mammary tumors and more cases of leukemia than the lower passages after ip injection. Cell-free extracts induced similar tumors. Not-infected control BMKC did not acquire the described properties. The nature of the induced MTV and MLV is discussed. (Author abstract) (57 Refs)

153. MOUSE MAMMARY TUMOR VIRUS IN HYBRIDS FROM STRAINS C57BL AND GR: BREEDING TEST OF BACKCROSS SEGREGANTS.

Heston WE, Smith B, Parks WP
Lab. Biology, NCI, NIH, Bethesda, MD 20014
J Exp Med; 144(4):1022-1030 1976

F1, F2, first backcross hybrids, and second backcross families of GR and C57BL mice were examined for the segregation of mouse mammary tumor viral (MMTV) expression. MMTV expression, as measured by double antibody radioimmunoassay from MMTV p14, segregated in 106 first backcross progeny at a 60:40 ratio; this was intermediate between what would be expected for either a single or two gene hypothesis. In female second backcross progeny of either male or female first backcross, a heterogeneous pattern of expression was noted that did not fit any simple Mendalian pattern. It appeared that all hybrid females contained MMTV proviral information that may be expressed either at late lactations or in a variable proportion of progeny mice. These findings are in agreement with a vertically transmitted genome regulated by multiple factors in these crosses. (20 Refs)

154. MURINE MAMMARY TUMOR CELL CLONES WITH VARYING DEGREES OF VIRUS EXPRESSION.

Parks WP, Scolnick EM
Natl. Cancer Inst., Bethesda, Md.
Virology; 55(1):163-173 1973

Viral expression by murine mammary tumor virus (MTV) may be detected by electron microscopy, tumor formation, antigen induction or nucleic acid hybridization. Using some of these methods a comparison was made of two single cell clones derived from Sykes' CC:-51, a type-B particle positive, type-C virus negative murine mammary tumor cell line. The clones had similar growth properties-they formed "dome-like" structures, grew in soft agar, and had abundant microvilli by electron microscopy-but differed markedly in their expression

of type-B viral information. One clone, clone 11, had morphological type-B particles, type-B specific sl antigen (3500 ng/mg protein), and cellular RNA which hybridized with MTV(3H)DNA product. The other clone, clone 6, did not have detectable particles by electron microscopy, antigen levels were below the limits of sensitivity or barely detectable (approximately 30 ng/mg protein), and RNA hybridizable to MTV DNA product was less than 5% of the reaction noted with the positive clone. Measurement of the cellular MTV-related DNA sequences by DNA-DNA hybridization using the same single-stranded MTV DNA sequences in both clones. Type-C viral expression (gs antigen and RNA levels) in both clones was comparable and not significantly higher than noted in other "normal" murine cell lines. The findings thus showed that there was a correlation between levels of viral antigen and hybridizable total cellular or polysomal RNA in these cells and that clones which contained equivalent amounts of MTV-related cellular DNA sequences had markedly different levels of hybridizable RNA, antigen, and virus particles. The results suggest that the mechanism of viral control in these cells is at the level of DNA to RNA transcription and is not necessarily dependent on presumable differentiated characteristics of mammary cells such as "doming".

155. RELATIONSHIP BETWEEN ORGANIZATION OF MAMMARY TUMORS AND THE ABILITY OF TUMOR CELLS TO REPLICATE MAMMARY TUMOR VIRUS AND TO RECOGNIZE GROWTH-INHIBITORY CONTACT SIGNALS IN VITRO.

McGrath CM, Nandi S, Young L
Dept. Zoology, U. California, Berkeley
J Virol; 9(2):367-376 1972

The relationship between mouse mammary tumor organization, organization of cultured mammary tumor cells, and replication of mammary tumor virus (MTV) was studied. MTV replication, shown by electron microscopic techniques, was confined primarily to cells organized as acini in intact mouse mammary glands. Primary mammary tumors maintained a high degree of acinar organization and cells therein continued to replicate MTV. Nonacinar mammary cells, derived by serial transplantation of acinar cells, no longer actively replicated MTV. This suggests that phenotypic differences exist among mammary epithelial cells in their ability to support virus replication, that a fundamental relationship exists between the organization of epithelium for secretion and active virus replication, and that this relationship is not altered as a primary consequence of neoplastic transformation. Mammary epithelial cells from pregnant, nontumor-bearing MTV-infected BALB/cfC3H mice, or from acinar mammary tumors from a number of mouse strains grown in culture under the influence of insulin or cortisol exhibited the ability to organize into discrete three-dimensional structures called "domes". MTV replication, determined by radioassay and indirect immunofluorescence, took place primarily in cells within these domes. Cells cultured from nonacinar tumors did not tend to organize into domes nor did they replicate MTV in primary culture. These results suggest that the cell organizational requirement for MTV replication observed in vivo is conserved in primary culture. Dome formation was not a result of virus replication, as uninfected BALB/c cells formed domes without MTV replication. Contact-dependent growth-regulatory signals (estimated from the saturation density of the culture) in non-MTV infected mammary epithelium cultures were not altered by virus active replication nor as a direct consequence of neoplastic transformation. Cells derived from nontumor BALB/cfC3H glands and from spontaneous tumors exhibited cell growth kinetics, saturation densities and DNA synthesis rates nearly identical to those of noninfected normal mammary epithelium in primary culture. Cultured nonalveolar tumor cells grew to higher-than-normal cell densities indicating altered growth regulatory signals.

156. EFFECTS OF CELL FUSION ON PRODUCTION OF THE MOUSE MAMMARY TUMOR VIRUS: IMMUNOFLUORESCENCE STUDY (MEETING ABSTRACT).

Lasfargues EY, Kramarsky B, Moore DH
Inst. Med. Res. Camden, N. J.
Proc Soc Exp Biol Med; 136(3):777-781 1971

Fusion of a cell line derived from a spontaneous mammary tumor in a (C57BL x Af) F1 hybrid mouse with two normal mammary cells lines, MG4 and RMG was induced with Sendai virus; 10 days later the mixed cell cultures and their controls were independently injected sc into newborn Amsterdam/IMR rats. Cells containing 2-5 nuclei were readily observed 1 day after fusion and were easily distinguished from the associated MG4 or RMG cells. Within 48 hr about 20% of the cells in the mammary tumor line MG4 population were multinucleated, with 7% being recognized as true heterokaryons. In the mammary tumor line RMG combination a total of 35% were multinucleated cells, with the ratio of heterokaryons roughly 1:3. After 10 days of cultivation nuclear enlargement, multilobulation, nuclear pulverization and chromatin fragmentation were noted in both fused cell populations; these features were rare in the neoplastic cell line and absent in normal cell lines. In the neoplastic line, fluorescein -labeling revealed 10-25% positive cells over a 1-yr period; neoplastic-MG4 fused cells revealed 63, 75, and 84% positive cells in 3 separate experiments in contrast to fusion with RMG rat-mammary cells which gave a ratio of 15, 18, and 28% positive cells. These results were confirmed by whole-cell mount electron microscopy. The findings indicated a significant increase of mammary tumor virus production when neoplastic cells were fused with normal mammary cells from the same species.

157. ULTRASTRUCTURAL AND QUANTITATIVE STUDIES OF MAMMARY TUMOR VIRUS PRODUCTION IN CULTURED MOUSE MAMMARY TUMOR CELLS.

Kramarsky B, Lasfargues EY, Moore DH
Inst. Med. Res., Camden, N. J.
Cancer Res; 30(4):1102-1108 1970

Budding mammary tumor virus (MTV) was compared with leukemia virus by use of a whole-cell-mounting method that allowed visualization of ultrastructural detail, including cores and surface spikes of budding virions. Binding of specific antibody to budding MTV virions was directly seen without use of conjugated antibody. Antibody was bound only to the virus bud and not to other regions of the cell membrane. Binding was not seen in control sera. Virus production in infected cells was assayed by the same method. The MMT/R-5 cell line had a higher ratio of producing cells than the MMT (Sykes) cell line (derived from a spontaneous mammary tumor), from which it was obtained by alternate in vivo-in vitro passage in Amsterdam rats. With aging of cultures, MMT productivity approached zero, but that of MMT/R-5 cells increased.

158. STIMULATION OF MAMMARY TUMOR VIRUS PRODUCTION IN A MOUSE MAMMARY TUMOR CELL LINE.

Lasfargues EY, Kramarsky B, Sarkar NH, Lasfargues JC, Pillsbury N, Moore DH
Inst. Med. Res., Camden, N. J.
Cancer Res; 30(4):1109-1117 1970

In a mouse mammary tumor cell line (MMT) that was alternately passaged through newborn mice (strains C57BL, Af and A) or newborn rats (Amsterdam/IMR) and tissue

culture, the passage of MMT cells into mice and back to tissue culture stimulated a 4-fold increase of Type B particle production by the cell line, but was subject to variations in successive subcultures. When passaged into rats, virus production increased 25-30-fold; virion budding remained constant and tumor-inducing capabilities were high through multiple subcultures. The greater stability in pH and stable growth rate of rat-passaged cells, suggested the possibility of production in tissue culture of a mammary tumor virus of greater purity and reliability than that obtained from milk or tumor extracts.

159. IN VITRO PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS IN A MOUSE MAMMARY TUMOR ASCITES LINE (MEETING ABSTRACT).

Keydar J, Gilead Z, Hartman JR, BenShaul Y
Dept. Microbiol., U. Tel Aviv, Israel
Proc Natl Acad Sci USA; 70(10):2983-2987 1973

An ascites line derived from a spontaneous mouse mammary carcinoma produces, on explantation and long-term cultivation in vitro, large amounts of oncornavirus particles. The yield of virus during the first and second day after explantation is low but increases to high levels after three to four days in culture. The yield of twice-purified virus was 1-2 mg/liter of medium. The virus seemed to be relatively free of C-type particles. The biochemical, biophysical, and electron microscopic characteristics of the virions are described. Molecular hybridization and immunological methods identify these virions as mouse mammary tumor virus.

160. SIMULTANEOUS CHEMICAL INDUCTION OF MTV AND MLV IN VITRO.

Links J, Calafat J, Buijs F, Tol O
Netherlands Cancer Inst., Div. Oncology, Sarphatistraat 108, Amsterdam, Netherlands
Eur J Cancer; 13(6):577-587 1977

Latent endogenous mammary tumor virus (MTV) and latent endogenous mouse leukemia virus (MLV) were simultaneously chemically induced with concomitant cell morphological alteration in tissue-cultured baby mouse kidney cells (BMKC) derived from the low mammary tumor mouse strains BALB/c (substrains He A and Crgl A) and C57BL/Li A. 3-Methylcholanthrene (MCA) was used with BMKC prepared from BALB/c/He A and BALB/c/Crgl A mice and 5-bromo-deoxyuridine(BrdU) with BMKC prepared from C57BL/Li A. Aggregates (pocks) of small rounded epithelial cells appeared on the BMKC monolayers several weeks after chemical treatment. Cell lines produced from single pocks released MTV (B-particles) and MLV (C-particles) as found with electron microscopy and reverse transcriptase determinations. All isolated cell lines grew well when serum was omitted from the medium. In female syngeneic BALB/c/He A mice, MCA altered BMKC-induced early (less than 300 days) mammary tumors and early (less than 200 days) leukemia. A cell-free extract from these chemically altered BMKC induced similar early tumors. Chemically non-treated control BMKC cultures did not show the described alterations and properties. The data support the conclusion that MTV can be present in "virus-free" mouse cells from which the virus can be chemically induced simultaneously with and in the same way as MLV. (Author abstract) (43 Refs)

161. TRANSFORMATION OF X/GF MOUSE EMBRYO CELL CULTURES TREATED WITH IODODEOXYURIDINE (MEETING ABSTRACT).

Goldfeder A, Stadler U
Cancer and Radiobiol. Res. Lab., Dept. of Biol., NY Univ., New York, NY 10032
Proc Am Assoc Cancer Res; 18:111 1977

This study was designed to detect the response of X/Gf mouse embryo cells to Iododeoxyuridine (IUdR) treatments. Three separate sublines were initiated from 12 and 18 day old embryos and tested periodically for spontaneous and IUdR induced virus production. Morphologic transformation was noted in one culture subline at passage 23. Cells of this transformed culture produced solid tumors upon implantation to newborn and to adult X/Gf mice. Tumor sections viewed by light microscopy showed sheets and bundles of spindle-shaped cells. Electron microscopic studies revealed cells with well preserved cytoplasmic organelles, the nuclei varied greatly in shape and size, some being multilobulated. No virus particles (C or MTV type) were ever noted electron microscopically in the tumor cells that were periodically passaged in X/Gf hosts. However, tests performed for reverse transcriptase gave positive results. This finding may indicate the presence of an endogenous oncogene which is not fully expressed in the transformed cells to produce a complete virus that could be visualized electron microscopically, or the X/Gf mice may possess an inhibitor (suppressor gene) preventing virus replication. Such a possibility may explain the resistance of X/Gf mice to spontaneous development of neoplasms. (Author Abstract)

162. INDEPENDENT POLYPEPTIDE CHAIN INITIATOR SITES FOR THE SYNTHESIS OF DIFFERENT CLASSES OF PROTEINS FOR AN RNA TUMOR VIRUS: MOUSE MAMMARY TUMOR VIRUS.

Schochetman G, Schlom J
Meloy Labs., Inc., Springfield, VA 22151
Virology; 73(2):431-441 1976

Hypertonicity produced by NaCl was found to inhibit cellular polypeptide chain initiation in mouse mammary tumor virus (MMTV)-infected Mm5mt/c1 cells reversibly. The hypertonic shock also selectively inhibited incorporation of H3- and C14-labeled amino acids into MMTV glycoproteins (gp 52 and gp 36) relative to MMTV nonglycoproteins (p28, p22, p18, p14, and p10) in completed virus particles. This reduced incorporation was due to selective inhibition of glycoprotein synthesis and not due to the production of glycoprotein-deficient virus particles nor to any posttranslational effects, as demonstrated by the fact that the buoyant density of MMTV produced in the presence of NaCl hypertonicity was identical to that of control MMTV. Particles devoid of their glycoproteins would have banded at a buoyant density of 1.14 g/ml and, moreover, the addition of excess NaCl to prelabeled Mm5mt/c1 cells had no effect on the relative amounts of prelabeled MMTV glycoproteins and nonglycoproteins appearing in completed virions. These data indicate that independent peptide chain initiation sites for viral-coded proteins may be a general property of all RNA tumor viruses. (34 Refs)

163. IDENTIFICATION OF THE BUDDING VIRIONS OF IN VITRO CULTURED L1210 LEUKEMIA CELLS BY IMMUNE ELECTRON MICROSCOPY (MEETING ABSTRACT).

Kramarsky B, Chen PL, Moore DH
Inst. Med. Res., Camden, N.J.
Proc Am Assoc Cancer Res; 15:96 1974

The morphology and morphogenesis of the virions of L1210 leukemia cells has been briefly described by Chopra et

al, and Chen et al. This cell line which was derived from a leukemia induced in a DBA2 mouse by methylcholanthrene treatment produces budding virions some of which appear to have characteristics of both MuMTV and MuLV. These virions are formed by the incorporation of a preformed A particle into a smooth envelope. The cells are positive for both MuMTV and MuLV antigen by immunofluorescence. In order to identify these virions positively we studied their ability to bind specifically to anti-MuMTV and/or anti-MuLV globulins by whole-cell-mount immunoelectron microscopy. No antibody binding was observed by the virions unless the cells were briefly fixed in 0.5% glutaraldehyde prior to their exposure to the antibody. In prefixed specimens the budding virions with preformed A particle cores specifically-bound anti-MuMTV and not anti MuLV globulin indicating that these virions are antigenically MTV.

164. FUSION OF XC RAT SARCOMA CELLS INDUCED BY MURINE LEUKAEMIA VIRUS-INFECTED MOUSE MAMMARY TUMOUR CELLS. ABSENCE OF INTERFERENCE BY SIMULTANEOUSLY SYNTHESIZED MAMMARY TUMOR VIRUS.

Svec J, Links J
Cancer Res. Inst., Bratislava, Czechoslovakia
Neoplasma; 20(6):699-703 1973

C3H mouse mammary tumor primary cultures were cocultivated with XC indicator cells pretreated with DEAE dextran; multinucleated syncytia characteristic for the action of murine leukemia virus (MuLV) were formed. To determine whether mouse mammary tumor virus (MTV) induces similar cytopathic effects in XC cells, the correlation between plaque formation activity and the presence or MuLV and MTV antigens was examined at various intervals after the seeding of tissue cultures with C3H mouse mammary tumor cells. The plaque forming activities of type-C-positive and type-C-negative mouse mammary tumor cell lines were also compared. The presence of plaque forming activity in the C3H mouse mammary cultures indicated the presence of MuLV antigens in these cells. Weak positivity in the XC test was also obtained in a few cultures showing no MuLV antigens. The full expression of the MuLV genome continued in 28-day-old cultures of C3H mammary tumor cells, in which the replication of MTV was suppressed. Finally, continuously produced MTV in the CLL-51 mammary tumor cell line, as well as purified and highly concentrated MTV, failed to induce syncytia and plaque formation in the indicator cell line. MTV does not appear to contain the heat-labile envelope lipoprotein which serves as the mediating factor in the MuLV-induced XC cell fusion. In addition, MuLV replicates independently from the expression of the MTV genome in mouse mammary tumors growing in vitro.

165. URETHAN AND X-RAY EFFECTS ON MICE OF A TUMOR-RESISTANT STRAIN, X/GF.

Goldfeder A
Dept. Hlth. Hosp., New York U., New York
Cancer Res; 32(12):2771-2777 1972

Inbred X/Gf mice with an extremely low incidence of spontaneous neoplasms were tested for their response to urethan and X-irradiation. Newborn, infant, and adult mice of both sexes were treated weekly with various doses of urethan (0.5 mg/g body weight (7 times) for newborn mice; .0 mg/g body weight (12 times) for infant and adult mice applied ip, and 24 mg/mouse/week applied cutaneously); with X-irradiation ranging from 300 rads (1 time) to 80 rads (10 times) and with combined treatments (urethan, 1.0 mg/g body weight (4 to 12 times) and X-irradiation, 75 to 150 rads (4 times)). The incidence of neoplasms was very low in all age groups regardless of the mode of treatment, and it reached 3.4% for the total of 1023 mice. The only statistically significant difference was noticed between the group subjected to combined treatments and pooled data on all experimental groups (p less than 0.05 for the "both-tail" test). Differences between other modes of treatment and between pooled data for both sexes were not statistically significant. Among 38 recorded type, 13 were thymomas of the lymphocytic type, three were reticulum cell sarcomas, and four were mammary tumors. The very low incidence of neoplasms induced by urethan and X-irradiation in X/Gf mice is explained on the basis of (a) their high endogenous immune competence, (b) the absence of leukemia viruses, and (c) the very low incidence of mammary tumor virus.

166. RADIORESISTANCE OF VIRUS FROM MURINE MAMMARY TUMORS AFTER GAMMA !RRADIATION.

Mouriquand J, Mouriguand MC, Mistry P, Gorka G
Centre d'Etudes Grenoble, Dept. Recherche Fondamentale, Lab. Biologie Cellulaire, Cedex 85, 38-Grenoble-Gare, Isere, France
C R Acad Sc Paris; 274:2259-2262 1972

Acellular extracts of mammary tumors from mice were irradiated with gamma radiation ranging from 150-1950 kiloR. Viral suspensions were obtained from the spontaneous mammary tumors of PS mice by Gross's method. After irradiation the suspensions were examined under the electron microscope for morphological changes of the virus particles. Before irradiation the virus was characterized by the presence of spicules. After irradiation the suspension was dense and coagulated, and the spicules were not observed. Three-wk-old mice were inoculated ip with the viral suspensions, and 229 females and 8 males (BALB/c/Orl) survived to 4 mo of age. Mice treated with nonirradiated control viruses developed tumors 74% of the time (av age 7 mo). Radiation of viruses at 150-450 kiloR produced a lower percentage of animals with tumors progressively with a minimum of 51.7% tumor occurrence at 450 kiloR. Viral radiation at 900-1950 kiloR increased the tumor incidence compared to the control group, with a max occurrence of 92% at 1200 kiloR. Type A virus particles were seen in the cytoplasm of mice inoculated with irradiated viruses, and type B particles were seen extracellularly. The RNA component of the virus B particle may have been affected by the gamma radiation. (16 Refs)

167. FURTHER STUDIES ON THE RADIORESISTANCE OF HIGHLY PURIFIED MOUSE MAMMARY TUMOR VIRUS.

Gorka C, Mouriquand J
Lab Biologie Cellulaire, Dept. Recherche Fondamentale, Centre d'Etudes Nucleaires Grenoble, B.P. 85 Centre de tri-38041 Grenoble Cedex, France
Eur J Cancer; 11:397-402 1975

The effects of high doses of gamma-rays, ranging from 1,080 to 3,960 kiloR, on cell free extracts from mammary tumors and highly purified mammary tumor virus (MTV) are compared. Mammary tumor occurrence as well as latency in BALB/c inoculated mice are not affected by the high doses used. Dilutions from 10**-2 to 10**-5 of irradiated samples are not followed by a decrease of biological activity, even at the dilution of 10**-5 which is characterized by a drop in the mammary tumor-inducing capacity of the non-irradiated control specimen. The incubation with ribonuclease crystalline (RNase), desoxyribonuclease (DNase) and pronase B grade (pronase) does not affect the biological activity of irradiated samples. Ultrastructural examination of irradiated virus suspensions shows very rare remnants of MTV compared to the typical aspect of the non-irradiated virus. (Author abstract) (23 Refs)

168. DIFFERENTIAL EFFECT OF IONIZING RADIATION ON MAMMARY TUMOR VIRUS ACTIVITY ASSOCIATED WITH BLOOD CELLS AND MAMMARY TUMOR CELLS.

Nandi S, Helmich C
Dept. Zool., Univ. Calif., Berkeley
J Natl Cancer Inst; 52(4):1271-1275 1974

169. MAMMARY TUMORS, PLAQUES, AND HYPERPLASTIC ALVEOLAR NODULES IN VARIOUS COMBINATIONS OF MOUSE INBRED STRAINS AND THE DIFFERENT LINES OF THE MAMMARY TUMOR VIRUS.

Heston WE, Vlahakis G
Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.
Int J Cancer; 7(1):141-148 1971

Mammary tumors were developed with frequencies ranging from less than 1 to 100% by each of the following inbred mouse strains: C3H, C3HfB, C3HfDD, C3H-Avy, C3H-AvyfB, DD, DDfB, DDf C3H, BALB/c BALB/cfDD, BALB/cfC3H, A(High), A(Low), AfB and C57BL. The highest incidence of mammary tumors was found in C3H-Avy mice (100%), and the lowest incidence (less than 1%) in A(Low) and C57BL mice; BALB/cfC3H mice also had 100% mammary tumor incidence. Low tumor incidence was found for AfB mice (1%) and DDfB mice (4%). While BALB/c mice had a tumor incidence of 97%. DDf C3H and C3H mice developed mammary tumors at the youngest average age of 6.8 and 7.2 months, resp; C3HfB and DDfB mice developed tumors at the highest average age, 18.8 and 19.5 months, resp. Mammary tumor virus antigen was found in all but 4 strains, DDfb, BALB/c, A(Low), and C3HfB. Mammary tumor viruses were found in the milk of 20/27 C3H mice and in 23/28 C3H-Avy mice; no virus was found in milk of C57BL or AfB mice. Virus plaques were the result of DD or BALB/c genotypes and DD virus but not of C3H or A genotype or of C3H or A virus. Hyperplastic alveolar nodules were found in all mouse strains developing mammary tumors; the age at which they first appeared depended on the mouse strain and on the line of virus; nodules appeared at the age of 3 months in DD, C3H and C3HfDD mice.

170. INHIBITION OF SPONTANEOUS MAMMARY CARCINOMA OF MICE BY TREATMENT WITH INTERFERON AND POLY I:C (MEETING ABSTRACT).

Came PE, Moore DH
Dept. Microbiol., Schering Corp., Bloomfield, N. J.
Proc Soc Exp Biol Med; 137(1):304-305 1971

Strain RIII mice were given 100 microg doses of polyinosinic acid: polycytidylic acid (poly I:C), 1000-2500 U interferon, normal mouse serum or no treatment (control), and the incidence of mammary tumor development and the appearance of mammary tumor virus in mammary milk were observed in the 4 treatment groups. Normal mouse serum did not reduce the incidence of spontaneous tumors from that seen in the control group; by 35 wk after treatment, nearly 100% of mice given normal serum had tumors. Poly I:C and interferon both inhibited the rate of tumor development; by 35 wk after treatment, only 60% of mice given poly I:C had developed tumors and a similar percentage of interferon-treated mice had developed tumors. Milk samples from mice in all 4 treatment groups were positive for mammary tumor virus.

171. REDUCED INCIDENCE OR SPONTANEOUS MAMMARY TUMORS IN C3H/HE MICE AFTER TREATMENT WITH POLYADENYLATE-POLYURIDYLATE.

Lacour F, Delage G, Chianale C
Immunol. Lab., Res. Group, CNRS Inst. Gustave Roussy, Villejuif, France
Science; 187(4173):256-257 1975

A study was made to determine whether admin of the double-standard polynucleotide complex polyadenylate;polyuridylate %poly(A);poly(U)% to newborn C3H/He mice could reduce the percentage of subsequently developing mammary tumors. The mammary tumors which appear in mature female mice represent the effect of a viral (mammary tumor virus, MTV) infection that occurs at birth. The two polynucleotides were mixed in equimolar ratios. New born C3H/He females received three i.p inj of 15 ug of poly(A);poly(U) on d. 1, 3, and 5 after birth. The mice were weaned 3 wk later. During the 380-d experimental period, 80 of the 127 control mice (63%) developed mammary tumors. Among those animals treated with the polynucleotides, 35/83 (42%) developed tumors during the same time period. This 21% difference is statistically very significant. The mortality rate in animals in which no tumor was found at the end of the observation or at death was essentially the same in control 29/47, as in treated 31/48 mic The tumor incidence among animals surviving 380 d was 58 % among the controls and 23% among the treated group, a significant difference. It is concluded that a significant reduction in the occurrence of mammary tumors is obtained when poly(A);poly(U) may induce a nonspecific stimulation of the immune response of the host to MTV. (11 refs)

IV. GENETIC STUDIES OF MuMTV

172. GENETIC TRANSMISSION OF VIRUSES THAT INCITE MAMMARY TUMOR IN MICE (MEETING ABSTRACT).

Bentvelzen P, Daams JH, Hageman P, Calafat J
Organization Hlth. Res., TNO, Rijswijk, Netherlands
Proc Natl Acad Sci USA; 67(1):377-384 1970

Three strains of untreated mice (Gr, C3Hf and BALB/c) and 2 strains of mice pretreated with irradiation or urethan (020 and C57BL) were infected with mammary tumor virus to investigate the genetic transmission of these viruses. In general, the viruses were transmitted vertically by the gametes of the mouse strain in which they naturally occurred. The virus was present in every cell, although often in an incomplete form. If a mammary tumor virus was introduced into a different mouse strain, only milkborne transmission occurred, after which the virus was found in a limited number of tissues. Mammary tumor viruses may be transmitted as genetic factors of the host strain to which they belong. A repressor, produced by a regulator gene, appears to control the rate of release of such a genetically transferred virus. Repression can be abrogated by a carcinogenic treatment. The repressor would also interfere with the replication of a superinfecting mammary tumor virus.

173. THE GENETICS OF RESISTANCE TO MAMMARY TUMOR VIRUS (MTV-S) IN C57BL/CRGL AND I/CRGL MICE.

Danilovs JA
Genetics Group and Cancer Research Laboratory, University of California, Berkeley, Ca. 94720
Proc Am Assoc Cancer Res; 17:26 1976

Mendelian segregation of genes responsible for resistance to MTV-S was studied in crosses between highly resistant C57BL and I inbred mice. (C57BL X I)F1 hybrids when foster

nursed by MTV-S infected C3H females are highly susceptible to MTV-S infection and mammary tumor development. F2, backcross, and second backcross females were foster nursed on C3H females and tested for some or all of the following traits present in C3H fostered F1 hybrids but not in C57BL/C3H or I/C3H parent strains: (a) ability to transmit viral infection to susceptible test animals via blood transfer, (b) ability to transmit viral infection at first parity to susceptible animals via milk, (c) appearance of viral antigen in milk detected by immunodiffusion, (d) development of mammary tumors, and (e) presence of hyperplastic alveolar nodules at autopsy (14 mo). The results from backcrosses to the C57BL show segregation of one recessive gene (Mtv-1) which has a primary role in resistance to MTV-S infection and one or more genes operating after infection to reduce tumor incidence in infected animals. Preliminary data suggest that Mtv-1 is linked to H-2. Backcrosses to the I mice suggest that two or more other genes are involved in that strain's resistance. (Author Abstract)

174. MECHANISM OF RESISTANCE TO MAMMARY TUMOR DEVELOPMENT IN C57BL AND I STRAINS OF MICE. II. INHERENT DIFFERENCES BETWEEN THE TWO STRAINS.

Nandi S
Cancer Res. Lab., U. California, Berkeley
J Natl Cancer Inst; 52(6):1797-1804 1974

Experiments were designed to follow the fate of mammary tumor virus (MTV) and host reactions to MTV and associated antigens in C57BL/Crgl (C57) and I/Crgl (I) mice. Introduction of C3H MTV into C57 and I mice, by transplantation of B-particle containing hyperplastic nodular outgrowth, resulted only in occasional milk transmission of MTV by these mice. However, (C57 X I)F1(F1) mice, exposed to MTV, could transmit virus serially in successive passages. After natural (foster-nursing) or artificial (inoculation or transplantation) introduction into C57, I, and F1 mice, MTV quickly disappeared in all three groups; thereafter, it remained undetectable in blood cells and hematopoietic tissues of C57 mice. MTV activity, however, reappeared rarely in blood cells and spleens of young I mice; such reappearance was always observed in blood cells of F1 mice beginning at about 3-4 wk of age. Production of blood cell-associated MTV and noduligenesis failed to occur, even under strong hormonal stimulation, in C57 mice implanted with C57 mammary nodular outgrowths capable of continuous production of MTV B particles. Noduligenesis did occur in F1 mice implanted with the same C57 nodular outgrowths. Transplanted I nodule outgrowths usually failed to establish or induce nodules in I hosts. After natural infection with MTV or after immunization with MTV-containing antigens, I, but not C57, mice developed virus-neutralizing antibodies. Few of the I nodules, when transplanted into untreated I host, survived and produced hyperactive outgrowths. However, a higher percentage of I nodules, when transplanted into I hosts treated with rabbit antimouse thymocyte serum, could produce hyperactive outgrowths. These results suggest that resistance of C57 mice to C3H virus-induced mammary tumorigenesis is due to the failure of the virus to cause adequate infection of hematopoietic cells, where nucleated blood cell-associated MTV is produced. The resistance of I mice to mammary tumorigenesis is probably due to their genetically determined high immunologic competence against MTV and associated antigens.

175. TRANSMISSION OF THE MAMMARY TUMOR VIRUS BY THE GR MOUSE STRAIN. II. GENETIC STUDIES.

Nandi S, Helmich C
Cancer Res. Lab., U. California, Berkeley, CA
J Natl Cancer Inst; 52(5):1567-1570 1974

The genetic basis of congenital transmission of mammary tumor virus (MTV) by GR females was studied with F1, F2, and backcross populations of GR X BALB/c (C-) mice. All mice were foster-nursed by MTV-free C-mothers. The occurrence of one or more of the three kinds of mammary lesions (pregnancy-dependent tumors, pregnancy-independent tumors, or hyperplastic nodules) in force-bred females within the first yr was considered an indication of MTV infection. A mouse without mammary lesions was still considered MTV-infected if she transmitted MTV through her milk. Of reciprocal F1 hybrids 100% developed mammary tumors by 7 months, and the incidence of mammary tumors in (GR X C-) X GR backcrosses was also close to 100%. From the criteria used to determine MTV infection, 75% of the (GR X C-) X C-backcross females were MTV-infected. Although mammary lesions were detected in only 77% of the F2:¢(GR X C-) X (GR X C-) populations, some lesion-free mice also transmitted MTV by milk. It was predicted that at least 90% of the F2 females were likely to be infected with MTV. The ratios of MTV-infected females in F1, F2, and backcross populations appeared compatible with the hypothesis that two independently segregating dominant genes in the GR mouse strain are involved in congenital transmission of its MTV, and that either one of these genes alone is adequate for MTV transmission.

176. GENETIC TRANSMISSION OF MAMMARY TUMOUR VIRUS BY GR MICE.

Van Nie R, Verstraeten AA, De Moes J
Div. Genetics, Antoni van Leeuwenhoekhuis, Netherlands Cancer Inst., Amsterdam, Netherlands
Int J Cancer; 19(3):383-390 1977

By immunodiffusion assay, milk samples of several strains of mice and of F1 hybrids of the GR strain were investigated for the presence of mammary tumor virus (MTV) antigens. When the exogenous MTV of the GR strain was introduced into BALB/c mice by foster-nursing, all milk samples of the first lactation period of these mice were negative. The presence of viral antigens in milk of the first lactation period was restricted to mice harboring endogenous MTV-GR. In the first backcross II population, BALB/c X (BALB/c X GR) X BALB/c, 33/51 mice, from immunodiffusion-positive mothers, had immunodiffusion-positive milk. However, only 1/71 mice, which were the progeny of immunodiffusion-negative backcross I mothers, was immunodiffusion-positive. A correlation was noted between the occurrence of both spontaneous mammary tumors before the age of 13 mo and early mammary tumors after hormone treatment and the presence of virus antigens in the milk. The early expression of virus antigens in the milk and the early appearance of mammary tumors in the GR strain seem to be controlled by the same genetic factors. (22 Refs)

177. GENETIC ANALYSIS OF MAMMARY TUMOR INDUCTION AND EXPRESSION OF MAMMARY TUMOR VIRUS ANTIGEN IN HORMONE-TREATED OVARIECTOMIZED GR MICE.

Van NIE R, Hilgers J
Department of Biology, The Netherlands Cancer Institute, Sarphatistraat 108, Amsterdam-1004, The Netherlands
J Natl Cancer Inst; 56(1):27-32 1976

Early stages of mammary tumors (EMT) were induced with a combined treatment of progesterone (p) and estrone (E) in ovariectomized adult GRS/ greater than A (GR) mice, a

strain of European origin and with a high incidence of mammary cancer. The mammary tumors were comparable to the pregnancy-dependent tumors of breeding females of this strain. The hormone treatment did not lead to EMT in a variety of other strains and only occasionally in the RIII and C3H strains. Treatment with P or E alone did not lead to EMT in GR mice, but treatment with the steroid compound 17.alpha-ethynyl-19-nortestosterone (ANT) did mimic the combined effect of P and E. Since EMT could be induced by ANT in all ovariectomized adult GR mice within 3 weeks, this tumor-induction method was suitable for analysis of the gene responsible for palpable, pregnancy-dependent mammary tumors of this strain. Another argument for the usefulness of this test for genetic analysis was the fact that, though mouse mammary tumor virus (MuMTV) of the GR strain was introduced into BALB/c and MAS mice by foster-nursing, ANT treatment did not lead to EMT. First and second backcross analyses showed that one gene was responsible for EMT induction. There was a strong correlation between the presence of EMT and MuMTV antigens in the mammary glands and milk of several first backcross populations between GR and other strains such as C57BL, BALB/c, DBAf, and C3Hf. This suggested that the expression of MuMTV antigens was also controlled by the EMT gene. Two types of resistance phenomena were observed. Neither type could prevent EMT after hormone treatment; however, they could delay EMT development. One resistance factor for EMT induction was noticeable and dominant in reciprocal hybrids of the GR and DBAf strains, whereas another resistance factor was detected in the backcross population only (i.e, in the C57BL x (C57BL x GR) backcross) and not in hybrids; therefore, this factor was recessive. Until now, linkage experiments with 18 markers to locate the gene for EMT induction in the map of the mouse were unsuccessful.

178. BALB/CFRIII: A NEW HIGH MAMMARY-TUMOR AND HIGH LEUKEMIA MOUSE STRAIN.

Squartini F, Bolis GB, Rossi G
Med. Sch., U. Pisa, Italy
J Natl Cancer Inst; 52(5):1635-1641 1974

A new inbred strain was established from a litter of BALB/c mice foster-nursed by RIII. This strain, BALB/cfRIII, carried the mammary tumor virus, received through RIII milk, and a leukemia virus. Accordingly, BALB/cfRIII mice showed a high incidence of mammary tumors and lymphatic leukemia. During the first 30 generations of inbreeding, 1292 BALB/cfRIII mice were observed. 463 males, 723 breeding females (573 normally bred and 150 force-bred), and 106 virgin females. The pattern of spontaneous tumorigenesis was as follows: mammary tumors: 18.9% at 571 days of age in virgin females, 75.2% at 324 days in normally bred females, and 85.3% at 237 days in force-bred females; lymphatic leukemia: 43.6% at 380 days in males, 58.5% at 446 days in virgin females, 15.9% at 343 days in normally bred females, and 13.3% at 282 days in force-bred females. Lung tumors (3%) and ovarian tumors were sporadically observed in old mice. Association oetween mammary tumors and leukemia was rare. Most mammary tumors were pregnancy dependent. These data are compared with those of the strain of origin BALB/c and the milk-donor strain RIII.

179. COMPARISON OF THREE MAMMARY TUMOR VIRUSES IN GENETICALLY SIMILAR SUSCEPTIBLE MICE.

Vlahakis G
Natl. Cancer Inst., Bethesda, Md.
J Natl Cancer Inst; 51(5):1711-1712 1973

Three naturally-occurring milk-borne mammary tumor viruses (MTVs) from the following inbred mouse strains were compared in genetically similar virgin and breeder BALB/cHe hosts which did not have MTV: C3H/He, A/He, and DD/He. In the absence of the hormones of pregnancy, the C3H-MTV was still effective in producing mammary tumors in susceptible BALB/c females; however, the tumors developed later and less frequently in the virgin hosts than in the breeders. Compared with BALB/cfC3H and BALB/cfCC breeders, mammary tumors in the BALB/cfA breeders were slightly reduced, but the difference between the BALB/cfDD and BALB/cfA breeders was not significant. The average age of tumor development was increased in the BALB/cfA mice, but only slightly compared with the BALB/cfDD animals. A-MTV was a weaker or less effective virus than C3H-MTV in producing mammary tumors in virgin females. Compared with both the C3H and A-MTVs, the MTV of DD is the weakest or least effective virus in the production of mammary tumors in virgin BALB/c females. Thus, the three MTVs differ in their oncogenic ability.

180. HISTOCOMPATIBILITY GENES (THE H-2 COMPLEX) AND SUSCEPTIBILITY TO MAMMARY TUMOR VIRUS IN MICE.

Muhlbock O, Dux A
Netherlands Cancer Inst., Amsterdam
J Natl Cancer Inst; 53(4):993-996 1974

Congenic strains of C57BL/10ScSn (H-2b) mice with the haplotypes H-2a, H-2d, H-2f, H-2i, H-2k, H-2m, H-2r, and H-2pa received mammary tumor virus (MTV) by foster-nursing on (C3H x 020)F1 females. After force breeding of mice, the mammary tumor incidence showed remarkable differences among strains. The strains with the haplotypes H-2b and H-2m were relatively resistant, while those with H-2f, H-2i, H-2d, and H-2a were highly susceptible. The others showed intermediate susceptibility. Comparison of the results, especially with the recombinant strains, indicated that genes in or near the D end of the H-2 locus determined the susceptibility to MTV: the subloci 2Db and 2Dq determined resistance, and 2Dd and 2Df determined high susceptibility.

181. HISTOCOMPATIBILITY GENES AND SUSCEPTIBILITY TO MAMMARY TUMOR VIRUS (MTV) IN MICE.

Muhlbock O, Dux A
Netherlands Cancer Inst., Amsterdam
Transplant Proc; 3(3):1247-1250 1971

Mammary tumor virus (MTV) has three different variants. Two of these variants have been investigated in this work: C3H-MTV, which is transmitted by the mothers' milk, and GR-MTV, transmitted at conception by either the sperm or the ovum. Congenic resistant (CR) strains and normal strains of the C57BL/10 mice were subjected to four separate experiments. In the first, newborn mice were given C3H-MTV by way of the milk. It was found that the CR-strains in which the H-2b allele of the B10-strain mice is replaced by the alleles 2a, 2d, 2f, 2k and 2m have a significantly higher incidence of tumor formation than both the B-10 strain and the CR-strains with H-2b allele but with different weak histocompatibility loci 1am, 1b, 3b, 8b and 9b. In the second experiment 2-month-old females of the CR-strain were injected ip with cell-free mammary tumor extract. Mammary tumor incidence was found to be higher in the females with the H-2 alleles 2a, 2f and 2m than in females with the H-2b allele. Replacing the different alleles at the weak histocompatibility loci had no influence. In the third experiment, GR-MTV was transmitted by males or females at conception to hybrid F1 mice. Hybrids of all CR strains had a high percentage of tumors, regardless of histocompatibility loci. Lastly, GR-MTV was given to newborn females through the lactation process. Females carrying the H-2b allele were found to be slightly more susceptible to tumors than those carrying other alleles. The

influence of the H-2 locus on the susceptibility to MTV is thus only apparent with C3H-MTV.

182. INHERITANCE OF SUSCEPTIBILITY TO ERYTHROCYTE-BORN BITTNER VIRUS IN MICE.

Nandi S, Haslam S, Helmich C
Cancer Res. Genet. Lab., U. California, Berkeley
Transplant Proc; 3(3):1251-1257 1971

A series of experiments designed to show the genetically determined susceptibility or resistance to the MTV (mouse mammary tumor virus) were conducted. The results confirmed previous reports that R-MTV causes significant infection in only strains that are histocompatible-2 (H-2) with respect to donors. It was found that mammary tissues are not refractory to allogenic R-MTV. Macrophage-rich peritoneal washing cells from mice immunized against H-2 antigens can significantly reduce R-MTV activity. Based on the results of this and previous studies a model explaining the fate of MTV in susceptible mice was suggested. MTV "B" particles, transported by maternal milk to the young, are carried by the hepatic portal system to the liver. Here the macrophages pick up the virus and transport it to the target cells in the hemopoietic system. R-MTV is produced in the hemopoietic cells and incorporated in the red blood cell fraction of the blood, which carries it until engulfed by macrophages; these then transport the R-MTV to target mammary cells prepared by hormones to render them infectible. The R-MTV then produces both nodule formation and B particles at the mammary tissue level.

183. A LOCUS AFFECTING CIRCULATING INTERFERON LEVELS INDUCED BY MOUSE MAMMARY TUMOR VIRUS.

De Mayer E, De Maeyer-Guignard J, Hall WT, Bailey DW
Inst. Radium, Univ. Paris-Sud, Orsay, France
J Gen Virol; 23(2):209-211 1974

A possible genetic influence on the production of virus-induced circulating interferon was investigated. C57BL/6, BALB c, F1 hybrid, F2 hybrid, and backcross mice were inoculated iv with C3H/He skim milk containing B-particles or with B-particle negative C57BL milk. The serum interferon levels were assayed at various intervals thereafter. The C57BL lines produced about three times as much interferon as did the BALB/c mice. The F1 hybrids were all low producers, while some of the F2 hybrids and backcrosses were low producers and some were high producers. Mendelian analysis, combined with the use of recombinant-inbred strains, indicated the existence of a locus with a quantitative effect on the circulating interferon levels induced by the mouse mammary tumor virus. This locus segregates independently from the locus which affects NDV-induced interferon levels (If-1) and has been tentatively designated iF-2.

V. IMMUNOLOGICAL STUDIES OF MuMTV

A. Immunological Assay Procedures

184. PROCEDURES FOR RADIOIMMUNOASSAY OF THE MOUSE MAMMARY TUMOR VIRUS.

Sheffield JB, Daly T, Dion AS, Taraschi N
Inst for Medical Research, Camden, NJ 08103
Cancer Res; 37(5):1480-1485 1977

A procedure for radioimmunoassay of the major glycoprotein antigen derived from murine mammary tumor virus is described. The assay is sensitive to 0.05 ng of antigen and is highly reproducible. The antigen, gp55, has been found to be group specific and will detect viruses in 13 separate mouse strains, as well as from continuous cell lines. Factors affecting the assay have been examined. (19 Refs) (Author Abstract)

185. RADIOIMMUNOASSAY FOR MOUSE MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGEN.

Lo-Gerfo P, Silverstein G, Charney J
Coll. Physicians Surgeons, Columbia, U., New York City
Surgery; 76(1):16-22 1974

Mouse mammary tumor virus (MTV) was isolated from Paris RIII/Haag milk and mouse mammary tumors, labeled with I125, and rebanded in sucrose density gradients at 1.18 g/ml. Using the rebanded, labeled, intact particles, a radioimmunoassay was developed for the detection of antigens associated with MTV. An inhibition double-antibody assay was employed which allowed detection of the viral antigen in a 1:25,000 dilution of RIII milk. The quantity of this viral associated antigen (VAA) in Paris RIII and C57BL milk was then determined. The Paris RIII mice shed large amounts of viral antigen into their milk even at early lactations. Milk from a tumor-free colony of C57BL mice contained detectable amounts of VAA. Although inhibition curves from the milk of these animals were similar to those obtained with purified virus, this finding does not indicate that the mice shed intact virus into their milk. The levels of VAA in a group of C57BL mice which had been inoculated with MTV during the neonatal period correlated with the eventual development of mammary tumors, making it possible to predict which animals were susceptible to tumor development. Inhibition curves with Tween-treated virus and intact virus suggest that envelope antigen was being detected by the assay.

186. QUANTITATION OF MOUSE MAMMARY TUMOR VIRUS (MTV) VIRIONS BY RADIOIMMUNOASSAY.

Cardiff RD
U. California, Sch. Med., Davis
J Immunol; 111(6):1722-1729 1973

The radioimmune precipitation (RIP) technique has been applied to the quantitation of the mouse mammary tumor virus (MTV); the MTV is externally labelled with radioiodine via the lactoperoxidase procedure. 125I-MTV derived from the milk or mammary tumor cells of BALB/cfC3H (MTV-infected) mice was co-precipitated, specifically in the presence of antibodies against MTV, by goat antibodies to rabbit IgG. The RIP of 125I-MTV was inhibited with unlabelled MTV, but it was not inhibited by cell-free extracts of host cell, milk, any of the murine C-type particles used, non-immune sera, or antibodies against BALB/c spleen cells. The assay reproducibility detected as little as 5 ng of intact virus. The serum inhibition of the RIP can be used to survey mice, rats, humans, and others for the presence or absence of anti-MTV antibodies, and the RIP system shows great potential for studying the antigenic relationships between closely related MTV substrains.

187. RADIOIMMUNOASSAY FOR MTV-ANTIGENS.

Verstraeten AA, Hageman PH, Kwa HG
Netherlands Cancer Inst., Amsterdam
Eur J Cancer; 9(2):155-157 1973

A quick, sensitive radioimmunoassay has been developed to detect mammary tumor virus (MTV)-specific antigens. The assay measures the degree of inhibition of binding of known 125I -labeled MTV antigens to rabbit anti-MTV antiserum preabsorbed to a sample of suspect plasma, milk or tumor extract. The assay detects two separate MTV antigens, one thought to be viral coat antigen and the other, viral nucleoid antigen. The assay is specific as no reaction occurs with plasma and mil samples from non-tumor-bearing BALB/c mice or with Rauscher leukemia virus extract. The assay is 10 to 300 times more sensitive in detecting the two MTV antigens than in the micro-Ouchterlony double-diffusion technique.

188. THE RADIOIMMUNOASSAY (RIA).

Van der Gugten AA
Netherlands Cancer Inst., Amsterdam, The Netherlands
Int Union Cancer Tech Rep Ser; 20:130-134 1975

A radioimmunoassay technique for determining prolactin concentrations in plasma and pituitaries is described. Prolactin is isolated from prolactin-producing pituitary tumors transplanted into rats (2-4 rats yield 100 mg prolactin). The tumor-bearing castrated male rats are treated with estrone to support tumor growth. The prolactin is chromatographed on DEAE-cellulose. An antiserum to rat prolactin is raised in the rabbit. The prolactin is labeled with ^{125}I by adding 1 mCi of $Na^{125}I$ and 25 ul of chloramine-T to 10 ul of the prolactin solution. After purification on Sephadex G-50 column, the prolactin is stored in 0.05 ml aliquots at -20 C until needed for the radioimmunoassay. Since the radioimmunoassay is based upon the competition between a labeled antigen and the unlabeled antigen for binding to a restricted number of antibodies, a method to separate bound from free labeled hormone is necessary; a commonly used technique is the double antibody method. The dilution of antiserum containing just enough antibodies to bind the labeled hormone nearly completely is used in the assay of competitive inhibition. The extent to which labeled prolactin and unlabeled prolactin compete for the limited number of binding sites on the antibody can be measured by incubation of a fixed amount of labeled antigen and the fixed dilution of antiserum with serial dilutions of unlabeled antigen. If the concentration of unlabeled antigen is plotted on a log scale and the percentage of radioactivity in the complex on a linear scale, a regression curve is obtained that becomes linear over a certain range. Reference curves for standard preparations are prepared and the amount of prolactin present in the plasma or pituitary homogenates is expressed as nanograms of the standard preparation. This method can be adapted to determine several antigens (mammary tumor virus or carcinoembryonic) of interest in cancer research.

189. THE PURIFICATION OF A GS ANTIGEN OF THE MURINE MAMMARY TUMOR VIRUS AND ITS QUANTITATION BY RADIOIMMUNOASSAY.

Ritzi E, Baldi A, Spiegelman S
Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., 701 West 168 St., New York, NY 10032
Virology; 75(1):188-197 1976

A method which uses concanavalin A (Con A) affinity chromatography for the purification of the mouse mammary tumor virus gs antigens gp52 and p27 is presented. Con A chromatography and DEAE cellulose fractionation are combined to yield the gs antigens in both high yield and sufficient purity for use in radioimmunoassay (RIA). The gp52 was iodinated with I125-Bolton-Hunter reagent, chromatographed on Sephadex G-100, and utilized in the development of a blocking RIA. The sensitivity of this assay (0.5 to 1.0 nanog) is superior to that of whole particle assays. The procedures used for the isolation and iodination of the gp52 avoid the technical problem of incomplete displacement of the I125-gp52 by native viral antigen. The RIA provides a sensitive, reliable tool for studying the expression of the gp52 antigen and its relationship to the onset and progression of murine breast cancer. (16 refs)

190. THE ROLE OF LEUKOCYTE SUBPOPULATIONS IN THE INDIRECT LEUKOCYTE ADHERENCE INHIBITION ASSAY IN THE MAMMARY TUMOR VIRUS SYSTEM.

Creemers P
Radiobiological Inst. TNO, 151 Lange Kleiweg, Rijswijk, The Netherlands
Eur J Immunol; 7:48-53 1977

A modified leukocyte adherence inhibition (LAI) test was developed to detect cellular immunologic reactivity of mice to the mammary tumor virus (MTV), which was isolated from BALB/cfC3H mammary tumors. DBA/2f mice, immunized ip with 1 ug of purified MTV, were used as positive control animals. Ten-week-old DBA/2f, BALB/c and C57BL mice served as normals. Leukocyte adherence inhibition factor (LAIF) was produced by spleen cells from immunized mice when cultured with antigen. LAIF was transferred to indicator cells for which peritoneal exudate cells from normal mice were used. In the indirect LAI assay, optimal MTV-specific LAIF production occurred after an incubation period of 24 hr when a cell concentration of 20 X 10^6/ml was employed. At least in the MTV system both T cells and adherent cells were necessary for producing LAIF, whose production strongly increased with prolonged incubation time. It was concluded that LAIF production occurred only when (a) adherent cells were incubated with the antigen; (b) the supernatant was transferred to T-cell-enriched cell populations; and (c) the supernatant of the latter was again transferred to adherent cells. (11 Refs)

191. IN VITRO IMMUNE RESPONSES TO VIRAL AND TUMOR ANTIGENS IN MURINE BREAST CANCER.

Sigel MM, Lopez DM, Ortiz-Muniz G
Laboratory of Virology, Department of Microbiology, University of Miami School of Medicine, Miami, Florida 33152
Cancer Res; 36(2):748-752 1976

Inhibition of migration of peritoneal exudate cells proved to be a useful measurement of cell-mediated immunity which correlated in several respects with blastogenic transformation reactions. Lectins (phytohemagglutinin and concanavalin A) inhibited the migration of peritoneal exudate cells from normal and tumor-bearing mice, whereas tumor antigen caused inhibition of migration of cells from tumor-bearing animals only. The disparity in immunogenic capacity previously observed with lymphocyte transformation studies was also manifested in migration inhibition, i.e. D1-DMBA-3 tumor being immunogenic and D1-DMBA-2 being nonimmunogenic. Using the migration inhibition and blastogenic transformation reactions, responses were obtained to mammary tumor virus (MTV) antigen(s) in cells from BALB/cCrgl mice, which are free of MTV. In contrast, cells from MTV-positive BALB/cfC3H mice failed to respond to this antigen(s) in both reactions, suggesting a form of tolerance. However, the reactions became positive after implantation with MTV-containing spontaneous mammary tumors. Two possible explanations of the origin of reactive lymphocytes, horizontal transmission, or activation of a gene coding for an MTV antigen(s), are discussed.

B. Immunological Studies of MuMTV Antigenic Determinants

192. MULTIPLE ANTIGENIC DETERMINANTS ON THE MAJOR SURFACE GLYCOPROTEIN OF MURINE MAMMARY TUMOR VIRUSES.

Teramoto YA, Kufe D, Schlom J
Div. Life Sciences, Meloy Lab., Springfield, VA 22151
Proc Natl Acad Sci USA; 74(8):3564-3568 1977

The major external protein of murine mammary tumor viruses (MMTVs) is a glycoprotein of mol wt 52,000 (gp52).

We report here that the gp52s of MMTVs from different mouse strains contain both type-specific and group-specific antigenic determinants. Competitive radioimmunoassays with externally labeled virion preparations were used to demonstrate that MMTV virions from C3H, RIII, and GR mice competed identically in "group-specific" assays but either competed with altered slopes or competed incompletely in the appropriate "type-specific" assays. Similar results were obtained with purified gp52 preparations as competitors. MMTVs of RIII, C3H, and GR mice, grown in feline cells, competed similarly to the corresponding murine-derived MMTVs, thus demonstrating that the observed type-specific and group-specific antigenic reactivities are viral coded. In competitive radioimmunoassays using an antiserum against MMTV of C3H mice that was preabsorbed with MMTV of GR mice, type-specific reactivities were further magnified; MMTV of C3H mice competed completely whereas no competition was observed with MMTV of GR mice as a competitor. These studies are in agreement with previous biological and molecular hybridization studies on the diversity of MMTVs from different mouse strains. (Author abstract) (25 Refs)

193. TYPE-SPECIFIC ANTIGENIC DETERMINANTS ON THE MAJOR EXTERNAL GLYCOPROTEIN OF HIGH- AND LOW-ONCOGENIC MURINE MAMMARY TUMOR VIRUSES.

Teramoto YA, Kufe D, Schlom J
Meloy Labs., Springfield, VA 22151
J Virol; 24(2):525-533 1977

Antisera prepared against mouse mammary tumor virus (MMTV) of C3H mice and externally labeled virions of the virus were used to distinguish between the gp52's of the high-oncogenic MMTV of C3H mice MMTV(C3H) and the low-oncogenic MMTV of the same strain MMTV(C3HF). The virions were obtained from the milk of RIII and C3HfC57BL mice and from culture fluids of primary mammary tumor cells. Comparison of the intact virion and purified gp52 radioimmunoassays showed that MMTV type-specific differences were enhanced with the intact virion radioimmunoassay. These differences were further magnified with appropriately absorbed antisera. The gp52's contained type-specific antigenic determinants. It is unlikely that the type-specific differences were due to differences in host-derived antigens or in host-coded glycosylation. The type-specific reactivities could be magnified by the use of an antisera dilution that does not give max sensitivity, use of the virion assay instead of the purified gp52 assay, and absorption of antisera with a particular strain of MMTV. (37 Refs)

194. SITES OF SYNTHESIS OF MURINE RNA TUMOR VIRUS (ONCORNAVIRUS) GROUP-SPECIFIC ANTIGENS.

Pattengale PK, Ikeda H, Thorbeck GJ
New York U. Sch. Med., N. Y.
Cancer Res; 34(4):810-817 1974

Autoradiography of immunoelectrophoretic patterns was used to study sites of synthesis of mammary tumor virus group-specific antigen (MTV-sl) and murine leukemia virus group-specific antigen (MuLV-gsl) protein in C3H and AKR mice of various ages. Synthesis of MTV-sl protein was seen only in the mammary gland of tumor-free late pregnant and lactating C3H mice. In addition, mammary tumors were strongly positive for production of MTV-sl antigen. Production of MuLV-gs protein was found in spleen, thymus, lymph node, placenta, mammary gland, testis, and ovary of nonleukemic AKR, as well as in some testis and ovary cultures of C3H mice. Leukemic AKR lymphoid tissue showed much stronger labeling of MuLV-gs than normal. In general, tissues that tended to have high extract titers for MuLV-gs protein as tested by immunofluorescent absorption also appeared positive with respect to synthesis, but some exceptions in this respect were noted.

195. MAMMARY TUM. VIRUS (MTV) ANTIGENS IN NORMAL AND MAMMARY TUMOR-BEARING MICE.

Hilgers JH, Theuns GJ, van Nie RV
Dept. Biol., Netherlands Cancer Inst., Amsterdam
Int J Cancer; 12(3):568-576 1973

Quantitative immunofluorescence tests were used to study MTV-antigen production in normal and mammary tumor-bearing mice of two low (BALB/c and C3Hf) and two high (C3H and GR) mammary cancer strains. Mammary tumors could be distinguished on the basis of MTV-antigen expression in two groups: (1) a group of positive and (2) a group of negative tumors occurring in BALB/c mice. While the tumors of the first group were all adenocarcinomas, the tumors of the second group were adenoacanthomas. MTV-antigen production was comparatively high in tumors of the C3Hf and C3H strains, as well as in the MTV-induced tumors of the BALB/c strain, but low in GR-strain tumors. Sera from mice bearing MTV-antigen producing mammary tumors (as well as from some pregnant and lactating GR mice) contained excess MTV-antigens. The spleens of BALB/c mice bearing MTV-induced tumors often contained detectable amounts of MTV-antigens, while normal and mammary tumor-bearing C3Hf and C3H mice also occasionally showed detectable amounts of MTV-antigens in their spleens. In contrast the spleens of GR mice were always MTV-antigen negative by immunofluorescence absorption tests. The thymuses, livers and kidneys of the various strains tested were invariably negative.

196. ANTIGENIC STRUCTURE OF MURINE MAMMARY TUMOUR VIRUSES.

Daams JH, Hageman P, Calafat J, Bentvelzen P
Netherlands Cancer Inst., Amsterdam
Eur J Cancer; 9(8):567-572 1973

Rabbit antisera against purified standard murine mammary tumor virus (MTV-S) precipitated the virions of four different virus strains in double immunodiffusion: MTV-S, -L, -P and -O. The sera detected eight soluble antigens of MTV-S and -O, but only five of -P and three of -L. The effect of trypsin, pepsin, HCl RNAse, phospholipase C, and acridine orange on the appearance of precipitation lines of MTV-S antigens were investigated. The results indicate that two soluble trypsin-sensitive antigens are located inside the nucleoid. They seem to contain some RNA fragments which do not influence antigenicity. They are group specific. Three other soluble antigens are membrane-constituents. Phospholipase C seems to increase their reactivity in immunodiffusion. They all contain a protein moiety which is essential for antigenicity. Two of the membrane antigens are involved in immunoprecipitation of the intact virion, one of them being group-specific.

197. MOUSE MAMMARY TUMOR VIRUS ANTIGEN (GP52): A MEANS FOR THE DETECTION OF TUMOR AND ASSESSMENT OF THERAPY (MEETING ABSTRACT).

Ritzi EM, Martin DS, Stolfi RL, Spiegelman S
Inst of Cancer Res, Columbia Univ, New York, NY 10032
Proc Am Assoc Cancer Res; 18:162 1977

The plasma level of the 52,000 MW glycoprotein of the murine mammary tumor virus, measured by radioimmunoassay, has been evaluated as a diagnostic signal for the presence of mammary neoplasia. In addition, this protein has been utilized for the assessment of disease status during and after tumor therapy. Plasma levels of the gp52 antigen were found to be approximately 100-fold higher in mice bearing spontaneously arising breast tumors than in mice from the

same colony which had not developed tumors. The gp52 level dropped quickly following surgical removal of the tumor, and sequential measurements during the postoperative period showed 100% correlation between elevation of gp52 level and tumor recurrence. Therapeutically predictive differences in plasma gp52 levels in animals treated with tumor surgery as compared to animals treated with tumor surgery plus combination chemotherapy (cytoxan + adriamycin + 5-fluorouracil) were detectable as early as 10 days after surgery and prior to tumor recurrence in either group. The gp52 level of mouse plasma can thus be utilized to predict therapeutic effect, evaluate therapeutic modalities, and aid in improving the management of human breast cancer. (Author Abstract)

198. EXPRESSION OF INDIVIDUAL PROTEINS OF MOUSE MAMMARY GLAND CANCER VIRUS IN TUMORS OF MAMMARY GLANDS IN MICE OF VARIOUS STRAINS.

Kryukova IN, Razvorotnev VA, Lavrovsky VA
N. F. Gamaleia Inst. Epidemiology Microbiology, USSR Acad. Medical Sciences, Moscow, USSR
Vopr Virusol; (5):580-584 1976

The expression of the main structural proteins of the mammary gland cancer viruses, gp52 and p27, were studied by means of immune sera to these proteins in homogenates of tumors from mice of low and high cancer lines. Protein gp52 was found in mice carrying MTV-S. No gp 52 was found in a fraction of purified type A particles from the cytoplasm of mammary gland tumors with the antiserum to p27; this fraction reacted to a line identical to that of the antigen from the C3HF mouse tumor. (18 refs)

199. STRAIN SPECIFICITY IN MOUSE MAMMARY TUMOR VIRUS VIRION ANTIGENS.

Blair PB
Cancer Res. Genetics Lab., U. California, Berkeley
Cancer Res; 31(10):1473-1477 1971

Immunodiffusion studies of mammary tumor virus (MTV) isolated from four strains of mice indicate that at least one antigen of the virion coat is common to all. At least six different antigens could be detected in one or more, but not all, of the four strains tested. It was concluded that the one common antigen was a group-specific antigen of the virion coat. Some of the remaining antigens detected may be considered to be type-specific antigens of the virion coat.

200. STUDIES ON ANTIGENIC CROSS-REACTIVITY OF ONCOGENIC RNA VIRUSES: CROSS-REACTIONS BETWEEN MOUSE MAMMARY TUMOR VIRUSES FROM DIFFERENT MOUSE STRAINS.

Blair PB, Weiss DW, Smith GH
Cancer Res. Genet. Lab., U. California, Berkeley, CA
Isr J Med Sci; 6(5):611-616 1970

Cross-reacting antigenicity between C3H/RIII and DBA strains of mammary tumor virus (MTV) and virus isolated from wild mice has been studied in infected mice from strains DBA, BALB/cfC3H, C3H and RIII. Test mice inoculated with either virus preparation combined with antisera against C3H, C3Hf, or C3H2 tissue did not develop mammary tumors within the test period compared to 3 of 12 females inoculated with RIII virus combined with antiserum against virus-free BALB/c tissue which developed tumors. Antisera from rabbits immunized with the virus-free BALB/c, C57Bl, or I tissue extracts did not neutralize the biologic activity of mammary tumor virus, while antisera from those animals immunized with virus obtained from BALB/cfC3H, BALB/cfDBA, BALB/cfRIII or BALB/cfWILD mice either completely or partially inactivated the biologic activity of the various MTV with only 3 of the 15 test animals developing nodules. In view of the many similarities between mammary tumor virus and various other oncogenic RNA virus, additional type-specific antigens may be present in the virion coat of the MTV.

201. IMMUNOLOGY OF THE MOUSE MAMMARY TUMOR VIRUS: COMPARISON OF THE ANTIGENICITY OF MAMMARY TUMOR VIRUS OBTAINED FROM SEVERAL STRAINS OF MICE.

Blair PB
U. California Cancer Res. Genet. Lab., Berkeley
Cancer Res; 30(3):625-631 1970

Antigenic properties of mammary tumor virus (MTV) strains derived from various mice were detected by use of the MTV antigen in immuno-diffusion studies using rabbit antisera. Cross-reactivity was shown in samples of a soluble MTV antigen from virus originally derived from GR, DBA, WILD, RIII, A, C3H or C3Hf mice. A similar cross-reacting antigenicity was found among preparations of MTV-B-particle preparations. MTV from C3Hf mice and from wild house mice lacked at least 1 antigenic component possessed by MTV from other sources, such as MTV of DBA or C3H origin. The significance of these antigenic similarities and differences is discussed.

202. DETECTION OF ANTIGENS OF THE MOUSE MAMMARY TUMOR (MTV) AND MURINE LEUKEMIA VIRUS (MULV) IN CELLS OF CULTURES DERIVED FROM MAMMARY TUMORS OF MICE OF SEVERAL STRAINS.

Hilgers J, Williams WC, Myers B, Dmochowski L
U. Texas M. D. Anderson Hosp. Tumor Inst., Houston
Virology; 45(2):470-483 1971

Cultured cells from eight mammary tumors of BALB/c, (C57BL x Af)F1, and RIII/Dm mice were reacted with each of three anti-mammary tumor virus (MTV) antisera prepared in rabbits, three anti-murine leukemia virus (MuLV) antisera prepared in rats, or one anti-feline leukemia virus antiserum prepared in rabbits. Cells contained MTV particles (MTV+ cells) or MuLV particles (MuLV+ cells), or lacked either or both particles (MTV- or MuLV- cells). Indirect immunofluorescence (IF) tests were used to detect anti-MTV and anti-MuLV antigens within cells, and mixed hemadsorption reaction tests (MHA) were used to detect anti-viral surface antigens. MTV- mammary tumor cells showed weak reactions or no reaction with anti-MTV sera in IF and MHA tests. MTV+ cells showed MHA titers as high as 1:1024 with anti-MTV antisera. When anti-MTV sera were tested in IF with either MuLV+ or MuLV- cells, no staining was seen. Some MTV- cells were positive for MuLV antigens in MHA and IF. One line was positive for MTV as well as MuLV antigens in both MHA and IF tests. Of five cell lines from BALB/c mammary tumors, three were positive for anti-MuLV antigens in MHA as well as IF tests. Type C virus particles were seen in all these three cell lines. No MTV antigen was found by IF in one line with an anti-MTV serum, but MHA showed some cells of this line positive for MTV antigen with the same anti-MTV serum. IF reactions were localized in cell cytoplasm; no nuclear fluorescence for MuLV and MTV antigens was observed. The MuLV-gs3 antigen (an antigen shared by mammalian leukemia-sarcoma viruses) was found by IF in tumor cells producing C-type particles. MuLV-gsl and MuLV-gs3 antigens were not seen in MTV+ cell lines which were MuLV-. Cell lines positive for MTV and/or MuLV antigens by IF were also positive by MHA. Anti-MuLV-gsl and anti-MuLV-gs3 antisera gave positive IF reactions with MuLV+ cells but negative MHA reactions with an MuLV+ cell line which produced C-type particles.

203. DEMONSTRATION BY THE ANTIGLOBULIN CONSUMPTION TEST WITH MURINE ANTISERA OF COMMON ANTIGENS IN TISSUES INFECTED WITH THE MAMMARY TUMOR VIRUS FROM DIFFERENT MOUSE STRAINS.

Holmes EC, Morton DL
Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.
J Natl Cancer Inst; 46(2):253-260 1971

Mammary tumor virus antigens were prepared from tumors in mice known to contain this virus, and anti-mammary tumor virus antisera were prepared by injection of histoincompatible mammary tumors induced by the virus into mammary tumor virus-free mice. In an antiglobulin consumption test, antisera were reacted against tissues infected with the mammary tumor virus, and absorption of the antimammary tumor virus antibody by some virus-infected tissues was observed. It was found that mammary tumor virus prepared from tumors carried by mouse strains C3H/HeN, DD/He, DBA/2JN, A/He, RIII/An, and BALB/cf appeared to share a common antigen related to the mammary tumor virus.

204. LOCALIZATION OF VIRAL ANTIGENS, DETERMINED BY IMMUNOPEROXIDASE, IN MAMMARY ADENOCARCINOMA IN MICE.

Thomas JA, Garzon S, Lambre C
Lab. Cell Biol., U. Paris, France
C R Acad Sci D (Paris); 277(4):457-462 1973

Immunoperoxidase staining was used to investigate viral antigens in three strains of mouse mammary adenocarcinoma. These strains were obtained by: (1) passage of the T III strain in Swiss mice and the consanguineous LAB subline, (2) passage of the T III strain in vitro, and (3) and reinoculation of the in vitro T III strain into LAB mice. Tumor slices induced by strain (1) were initially peroxidase-positive, but became peroxidase-negative starting with the 52nd passage when no A or B particles were present; these cells have remained negative up to the 91st passage. Cells infected with strain (2) contained no A or B particles and were peroxidase-negative between the 359th and 375th passages. Tumors induced with strain (3) were very positive: peroxidase was present in the cytoplasm, on apical cell membranes, and inside the galactophoric canals. The location of peroxidase-positive structures and their number in the cells corresponded to the location and number of A and B particles of mouse mammary tumor virus.

205. ANTIGENICALLY DISTINCT FORMS OF MAMMARY TUMOR VIRUS 'N BLOOD AND MAMMARY TISSUES OF MICE.

Nandi S, Haslam S, Aldrich CD
Dept. Zool., U. California, Berkeley
J Natl Cancer Inst; 46(5):1035-1038 1971

Mammary tumor virus (MTV) antigens from mammary tissue or milk from BALB/cfC3H/Crgl (C+) mice with Freund's adjuvant were used to immunize syngeneic adult female C+ mice and New Zealand White rabbits by ip injection on day 1 and without adjuvant on days 30 and 68. The mice were bled on day 90 and pooled sera from 3 separate sets of rabbits were heat-inactivated by incubation at 56 C for 30 min and subsequently adsorbed in vitro with RBC from MTV-free (C-) mice. Both mouse and rabbit antisera against MTV neutralized mouse MTV but not rabbit MTV. Of 44 mice injected with virus incubated with antisera against B particles and tumor extracts from C+ mice, 7% developed an average of 2 nodules per mouse, whereas 34 of 39 mice, or 87% developed an average of 19 nodules in the control groups. In contrast, rabbit MTV incubated in the same antisera induced an average of 31 nodules per mouse among 26 of 37 mice, or 70% compared to an average of 25 nodules among 17 of 27 control mice, or 63%. Results indicate that MTV activity in mammary tissue extracts, but not in hemolyzed RBC preparations, can be neutralized by syngeneic or allogeneic mouse or rabbit antisera against virus preparations from milk or mammary tumors.

206. BINDING OF CONCANAVALIN A TO THE ENVELOPE OF TWO MURINE RNA TUMOUR VIRUSES.

Calafat J, Hageman PC
Netherlands Cancer Inst., Amsterdam
J Gen Virol; 14:103-106 1972

The binding of concanavalin A (Con A) to the envelope of two RNA tumor viruses that mature at the cell membrane was studied by electron microscopy. B particles of the mouse mammary tumor virus (MTV-s) were purified from mammary tumors of BALB/cDEAfC3H/HeA or C3H/HeA mice. C particles of Rauscher murine leukemia virus (RMLV) were purified from the spleens of infected BALB/cDEA mice. Particles were fixed and incubated with 125-5000 microg/ml Con A for 10, 30, or 60 min at room temperature. The particle-Con A complexes were stained with 1% PTA. Both B and C particles were agglutinated in groups by Con A, and there was a thick layer of electron-dense, fairly homogeneous precipitate along the virus membrane. When 0.1M alpha-methyl-D-glucoside, a sugar that competes with Con A for binding sites, was added, practically no agglutination or precipitate was seen. Virus treated with peroxidase alone followed by the diaminobenzidine reaction showed no attached precipitate. After negative staining, Con A was seen attached to virus particles. B particles incubated with anti-B particle serum also agglutinated, with antibody covering the virus envelope, indicating that RNA tumor viruses themselves may contribute to the surface changes in tumor cells.

207. CORRELATION OF IN VITRO AND IN VIVO STUDIES OF ANTIGENS RELEVANT TO THE CONTROL OF MURINE BREAST CANCER.

Stutman O
Cellular Immunobiology Section, Memorial Sloan-Kettering Cancer Center, NY, NY 10021
Cancer Res; 36(2):739-747 1976

The specific immune response of C3H (mammary tumor virus (MTV)) (MTV+) and C3Hf sublines (MTV- or milk-MTV-) to mammary tumors of C3H origin was measured in vitro by the ability of lymphocytes derived from immunized animals to destroy ^{3}H-proline prelabeled target cells after 36 hr of incubation in vitro (lymphocyte:target ratio, 400:1). Primary cytotoxic responses were obtained both in C3H and C3Hf mice and were mediated mainly by T-lymphocytes (Thy.1-positive cells). The degree of cross-reactivity between different C3H mammary tumors showed wide ranges and actually depended on the amounts of MTV-related antigens expressed in the tumor cells. An inverse relationship between MTV-related and H2 histocompatibility antigens was observed. Thy.1.2 antigen (.theta-C3H) was also detected on the surface of mammary tumor cells. Both C3H and C3Hf recognized cross-reacting and noncross-reacting antigens in the tumor cells, although the magnitude of the response in the MTV+ mice was lower than in the C3Hf sublines. Soluble antigens could be extracted by 3 M KCl treatment of the tumor cells and could be used as immunogens (eliciting cytotoxic responses against mammary tumor cells), or as stimulators for thymidine uptake (blast transformation in vitro) for specifically immune T-lymphocytes. Attempts to modify spontaneous tumor development in C3H and C3HfA virgin female mice by immunization with formalinized MTV or with soluble antigens extracted from C3H mammary tumors, although still in progress, showed a moderate preventive effect (especially in the C3HfA) immunized with MTV and an

acceleration of tumor appearance both in C3H and C3HfA mice immunized with the soluble antigens extracted from C3H mammary tumors. This last set of results, although preliminary, indicates that a better understanding of the immunological events in this system is essential for the design of experiments of prophylaxis of tumor development.

208. IN VITRO LYMPHOCYTE SENSITIZATION TO SYNGENEIC TARGET CELLS.

Wei WZ, Heppner GH
Dept. of Medicine, Roger Williams General Hospital, Brown Univ., Providence, R.I. 02908
Proc Am Assoc Cancer Res; 17:21 1976

To better understand and control the development of cell-mediated immunity to mouse mammary tumors, we are studying lymphocyte sensitization in vitro. Both MTV positive and negative mammary tumors and fibroblasts of strain BALB/c mice are grown to near confluency in monolayer cultures in Falcon #3013 flasks and then irradiated with 3000r. 30x10⁶ lymph node cells (LNC) from normal syngeneic mice are introduced into the culture flasks. The culture are incubated for 5-6 days at 37 degrees C in a 5% CO2 in air atmosphere in RPMI 1640 medium plus 15% fetal calf serum, non-essential amino acids, glutamine, antibiotics, and 5x10**-5M mercaptoethanol. The LNC are harvested from the cultures and tested in a criss-cross fashion by microcytotoxicity assay for toxicity to the sensitizing cells. So far little evidence for specific sensitization to tumor antigens has been obtained. Rather, LNC sensitized by either type of tumor are generally cytotoxic to both the tumor cells and normal fibroblasts and vice versa. Occasionally, target cell survival is better after treatment with sensitized LNC than after normal LNC, but again this is not specific for tumor cell targets. These results are comparable to those obtained by others with human tumors (Int J Cancer 15:342, 1975). (Author Abstract)

209. IMMUNOLOGICAL STUDIES ON MOUSE MAMMARY TUMORS AND LEUKEMIA.

Dmochowki L, Williams WC, Swearingen GR, Myers B, Fujinaga S
U. Texas M.D. Anderson Hosp. Tumor Inst., Houston
Tex Rep Biol Med; 29(1):41-62 1971

Intravenous inoculation of New Zealand white rabbits with mouse mammary tumor virus (MTV) from milk of RIII/Dm and of A/Dm high-mammary-cancer strain mice produced immune sera that appeared to be specific for the whole MTV virion. One of the precipitate lines produced by the anti-MTV sera against MTV antigens from milk of these 2 strains contained characteristic type B (or MTV) particles. This precipitate line was not removable by absorption with tissue preparations from low-mammary-cancer strain mice; its appearance was found to be prevented upon testing of the immune sera against milk of mice with low incidence of mammary cancer (BALB/C/Dm or C57BL/6/Dm). Immunodiffusion tests revealed a similarity of the MTV from different strains of mice. The anti-MTV serum gave a positive mixed hemadsorption reaction (MHA) with both spontaneous and induced mouse mammary tumors containing MTV (type B particles) and/or MLV (type C particles). A negative MHA reaction occurred with a cell line derived from an induced mammary tumor in a BALB/c/Dm strain mouse where no type B or type C virus particles could be found by electron microscopy. Positive MHA reactions with the anti-MTV serum were obtained with cultures of leukemic tissues, of mouse embryos and of a 3-methylcholanthrene -induced mouse sarcoma, all shown to contain type C particles. The MHA reaction of the investigation anti-MTV serum appeared to be specific for both MTV and MLV. Positive MHA reactions were given also by an anti-MLV serum with cultures of leukemic tissues, mouse mammary tumors and mouse embryo tissues containing type C particles; this reaction appeared to be due to the presence of antibodies to heterophile and viral antigens in MLV infected tissues. The positive MHA reaction given by anti-MTV and anti-MLV sera with tissues containing both type B and type C particles indicates the presence of antibodies to type C particles in the investigated anti-MTV sera and the widespread presence of MLV.

210. PSEUDOTYPES OF VESICULAR STOMATITIS VIRUS WITH ENVELOPE ANTIGENS PROVIDED BY MURINE MAMMARY TUMOR VIRUS.

Zavada J, Dickson C, Weiss R
Imperial Cancer Res. Fund Labs., Post Office Box 123, Lincoln's Inn Fields, London, WC2A 3PX, England
Virology; (281):221-231 1977

When infected with vesicular stomatitis virus (VSV), mammary tumor cells derived from spontaneous tumors of GR and C3H mice produced at least two types of particles containing the VSV genome but expressing different envelope characteristics (VSV pseudotypes). One of these VSV pseudotypes was infectious for normal mouse mammary epithelial cells and mouse embryo cells but noninfectious for mouse 3T3 cells, mink lung cells, and Vero cells. When the mammary tumor cells were treated with dexamethasone prior to VSV infection, the titer of this pseudotype increased significantly. In contrast, the second pseudotype was infectious for mink cells but not for the other cell lines tested; the titer of this pseudotype was unaffected by dexamethasone. The first pseudotype was almost completely neutralized by murine mammary tumor virus (MuMTV) antiserum, but the second pseudotype was only partially neutralized at a higher antiserum concentration. Neither pseudotype showed the neutralization, host range, or interference properties of either ecotropic or xenotropic murine C-type viruses. These results suggest that the first pseudotype is VSV(MuMTV). The other pseudotype is less well defined but it may be a xenotropic MuMTV. A filterable agent isolated from GR mammary carcinoma cultures was able to reactivate the infectivity of VSV neutralized by antiserum. This agent, which may represent an unknown contaminating virus, was transmissible to mink cells. (38 Refs)

211. IMMUNOLOGIC STUDIES OF THE LOW MOLECULAR WEIGHT DNA BINDING PROTEIN OF MURINE ONCORNAVIRUSES.

Long CW, Berzinski R, Gilden RV
Viral Oncology Program, NCI-Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21701
Int J Cancer; 19(6):843-850 1977

A low molecular wt, highly basic DNA-binding protein was purified from several oncornaviruses by the sequential procedures of gel filtration in guanidine-hydrochloride, DEAE-cellulose chromatography and affinity chromatography on single-stranded DNA sepharose. The binding protein from Rauscher and woolly monkey type-C viruses was the fastest migrating of the virion proteins in SDS-polyacrylamide gels and thus is designated p10 according to previous convention although our estimates of molecular wt were 8-9,000 daltons. The binding protein from these two viruses was resolved into two bands by acid-urea electrophoresis although only a single NH2 terminal amino acid was detected, thus indicating charge heterogeneity. Antibody to Rauscher virus p10 species-specific in gel diffusion and complement-fixation tests did not exhibit cross-reactivity with other virion proteins. A DNA-binding protein was also detected in preparations of mouse mammary tumor virus. This purified protein had an apparent molecular wt of 12,500, was the second fastest migrating component in the virus

preparations, and was antigenically unrelated to the mouse type-C virus p10. (Author abstract) (20 Refs)

C. Autogenous Immunity to MuMTV and MuMTV-Induced Tumors

212. AUTOGENOUS IMMUNITY TO MOUSE MAMMARY TUMOR VIRUS IN MOUSE STRAINS OF HIGH AND LOW MAMMARY TUMOR INCIDENCE.

Ihle JN, Arthur LO, Fine DL
Basic Research and Viral Oncology Programs, National Cancer Institute Frederick Cancer Research Center, Frederick, Maryland 21701
Cancer Res; 36(8):2840-2844 1976

Specific radioimmune precipitation assays were utilized to demonstrate the presence of precipitating antibodies to mouse mammary tumor virus (MMTV) in the high-spontaneous mammary tumor strains of mice: C3H/HeN**+, GR/N, BALB/cfC3H, and C57BL/6 x C3H F1 (hereafter called B6C3F1). Antibody titers in C3H/HeN**+ mice increased with age, with highest titers observed in tumor-bearing animals. MMTV-precipitating antibodies were not detectable by radioimmune precipitation assay in low-mammary tumor strains (AKR, BALB/c, C57BL/6, and C3H/HeN**-) but were detectable in MMTV-inoculated BALB/c mice. Appearance of antibodies preceded palpable tumor formation, and antibody titers were directly correlated to virus dose. Natural antibody to MMTV in C3H/HeN**+ and B6C3F1 mice coexists with the murine leukemia virus natural antibody as determined by competition radioimmunoassays. (Author Abstract)

213. ANTIBODY-INDUCED MODULATION AND SHEDDING OF MAMMARY TUMOR VIRUS ANTIGENS ON THE SURFACES OF GR ASCITES LEUKEMIA CELLS AS COMPARED WITH NORMAL ANTIGENS.

Calafat J, Hilgers J, Van Blitterswijk WJ, Verbeet M, Hageman PC
Dept. Electron Microscopy, The Netherlands Cancer Inst., Sarphatistraat 108, Amsterdam, The Netherlands
J Natl Cancer Inst; 56(5):10191029 1976

The distribution, antibody-induced redistribution, and shedding of murine mammary tumor virus (MuMTV) antigens on the surfaces of GR mouse ascites leukemia (GRSL) cells were studied by the immunoferritin technique and compared with the same activities of Thy 1.2 and H-2.8 antigens. MuMTV antigens were redistributed easily and then largely shed from the cell surface, H-2.8 antigen moved easily and probably was partially released from the plasma membrane, and Thy 1.2 antigen moved slowly. No shedding of Thy 1.2 antigen from the cell surface occurred, but some interiorization was found. The complement-dependent cytotoxicity test was used to study the possibility of antigenic modulation for these cell-surface antigens. MuMTV antigens from the surface of the GRSL cells could be modulated by preincubation with anti-MuMTV serum, in contrast to H-2.8 and Thy 1.2 antigens. The results obtained with the immunoferritin technique and the cytotoxicity test correlated well and suggested that shedding of MuMTV antigens from the cell surfaces may occur in vivo, providing a way for the tumor to escape from the immune defense of the host. Thy 1.2 and H-2.8 antigens were present on the envelope of B and C particles, which suggested that these viruses do not select a Thy 1.2 or H-2.8-negative area of the GRSL cell surface as a maturation site. (18 refs)

214. CELLULAR IMMUNITY TO THE MAMMARY TUMOUR VIRUS IN MICE BEARING PRIMARY MAMMARY TUMOURS.

Creemers P, Bentvelzen P
Radiobiological Inst. TNO, Lange Kleiweg 151, Rijswijk, ZH, Netherlands
Eur J Cancer; 13(6):503-510 1977

The development of cellular immunity directed against the murine mammary tumor virus (MTV) during the growth of primary mammary tumors has been studied in BALB/c, BALB/cfC3H and GR mice by measuring WBC stimulation and WBC adherence inhibition in the presence of purified MTV. WBC react against group-specific antigens of different MTV strains in these assays. Purified Rauscher murine leukemia virus was used as a control. In both assays, MTV-specific reactivity peaked at a tumor wt of about 1 g; afterwards, it almost completely disappeared. It increased again to about half the original level when the tumor reached a wt of about 3 g. Peak blastogenesis of lymph node cells was observed at a tumor wt somewhat higher than when peak blastogenesis of spleen cells occurred. The possible causes of the general decrease and oscillation in the cellular immune response during tumor growth are discussed. (Author abstract) (32 Refs)

215. MACROPHAGE MIGRATION INHIBITION AND LYMPHOCYTE STIMULATION WITH MAMMARY TUMOR VIRUS ASSOCIATED ANTIGENS IN BALB/C MICE (39179) (MEETING ABSTRACT).

Lopez DM, Ortiz-Muniz G, Sigel MM
Univ. Miami Sch. Medicine, P.O. Box 520875, Biscayne Annex, Miami, FL 33152
Proc Soc Exp Biol Med; 151(1):225-230 1976

Lymphocytes of BALB/c mice, which had been believed to be devoid of mammary tumor virus (MTV) by several criteria, demonstrated sensitivity to MTV antigens in blastogenic transformation and migration inhibition assays. The cause of this unexpected sensitivity was uncertain, but may have been related to horizontal transmission of MTV or to the selective derepression of certain portions of vertically-transmitted viral genomes. Lymphocytes from MTV-positive BALB/cfC3H mice were not sensitive to MTV antigens, unless derived from mice that had been implanted with MTV-positive tumors. These findings suggest either that there was a state of tolerance to MTV antigens which was broken by the tumor transplant, or that responses were directed towards antigens to which the host is not tolerant.

216. SPONTANEOUS AGE-DEPENDENT PRODUCTION OF ANTIBODIES AGAINST THE VIRION IN CBA/BLN MICE INFECTED NEONATALLY WITH THE MAMMARY TUMOUR VIRUS (MTV).

Zotter S, Muller M, Grossmann H
Med. Acad. "Carl Gustave Carus," Dresden, E. Germany
Exp Pathol (Jena); 8(2):115-121 1973

Spontaneous occurrence of antibodies to the mammary tumor virus (MTV) B-particle was studied in naturally MTV-infected CBA/Bln mice of different ages. The micro-Ouchterlony immunodiffusion assay and the indirect immunofluorescence test were used. In the immunofluorescence assay, spontaneous anti-MTV antibodies were revealed in all tested sera from adult MTV-bearing animals, while the micro-Ouchterlony technique gave positive results for only 31 of 108 sera. In the immunodiffusion assay, the number of positive sera in adult females increased with age but was not significantly influenced by the number of litters/animal. Immunofluorescence studies on newborns immediately after birth and on several foster-nursed infant mice showed that the antibody is transmitted in utero as well as by milk. Young

mice MTV-infected by milk seem to start production of antibodies at age 3 or 4 wk and for that reason induction of antibody formation may take place during virus penetration into the lymphatic system and/or in the stage of viremia. It is concluded that the antibody response after MTV infection is the most sensitive criterion of MTV infection in CBA mice.

217. MAMMARY TUMOR VIRUS (MTV) INFECTION OF CBA/BLN MICE INVOLVING PRODUCTION OF ANTIBODIES TO MTV.

Muller M, Zotter S
Carl Gustav Carus Med. Acad., Dresden, Germany
J Natl Cancer Inst; 50(3):713-717 1973

With acetone -fixed, frozen-cut slices of syngeneically grafted CBA/Bln murine mammary tumors extremely rich in mammary tumor virus (MTV) A and B particles, spontaneously occurring antibodies could be detected in 43 of 46 MTV-infected mice by means of the indirect immunofluorescent technique. These antibodies were found in male and female MTV-infected CBA/Bln and XVII/Bln mice but not in MTV-free mice of both strains. The antibodies could be absorbed totally by MTV-containing milks of the two strains, whereas MTV-free milks of both strains failed to do so. In correspondence to the specificity of precipitating antibodies detectable in a limited number of infected mice, which are directed against the B particles or an antigen of the outer viral coat, the resulting fluorescence was restricted to the intercellular spaces and glandular lumina of the tumor tissue. The results show that no trace of any true immunologic tolerance to this particular MTV antigen is established in CBA/Bln mice. Furthermore, this type of antibody response seems to be the most sensitive indicator for an MTV infection.

218. NATURALLY OCCURRING LYMPHOCYTE REACTIVITY TO PURIFIED MAMMARY TUMOR VIRUS ANTIGENS.

Gillette RW, Lowery LT
Cancer Center of Hawaii, University of Hawaii, Honolulu, Hawaii 96822
J Reticuloendothel Soc; 21(1):1-6 1977

Spleen cells from high (RIII and C3H/He) and low (NIH Swiss) MTV-expressing strains of mice responded to the presence of mammary tumor virus (MTV) Ags. Spleen cells from newborn donors did not react to MTV Ags. The direct and indirect migration inhibition assays were also used to demonstrate reactivity to Ags from disrupted MTV virions. In the presence of MTV Ags, lymphocytes from both high and low MTV expressing strains of mice produced factors that inhibited the migration of syngeneic peritoneal cells. Spleen cells from animals carrying advanced spontaneous mammary adenocarcinomas were in some instances hyporesponsive to MTV Ags while spleen cells from mice with small mammary tumors were uniformly reactive to MTV Ags. The data suggest that mammary tumors progress in the face of a significant immune response to MTV. (17 Refs) (Author Abstract)

219. IMMUNOFLUORESCENT DETECTION OF SPONTANEOUSLY OCCURRING ANTIBODIES IN MICE TO INTRACYTOPLASMIC A PARTICLES (IAP) OF MOUSE MAMMARY TUMOURS.

Zotter S, Muller M
Medical Academy "Carl Gustav Carus" Dresden. Institute of Pathology
Exp Pathol (Jena); 12(5):223-227 1976

By means of the indirect immunofluorescence technique, so-called spontaneously occurring antibodies in mice were detected specifically reacting with iAP of mouse mammary tumours. The specificity of the mouse antibody reaction was supported by blocking with rabbit anti iAp antiserum and by absorption with purified iAP preparations and mammary tumour virus (MTV)-containing materials. A partial correlation was found between the antibody frequencies in various mouse strains and the strain-specific mammary tumour incidence. Some mice of strains hitherto regarded as "MTV-free" were also shown to possess anti iAp antibodies, presumably indicating expression of MTV antigens coded by the genetically integrated MTV. The antibodies are produced spontaneously in (virgin) females as well as in male mice. (Author Abstract)

220. VIRUS ONCOGENESIS AND TUMOR IMMUNOGENICITY IN THE MOUSE MAMMARY TUMOR SYSTEM.

Vaage J, Medina D
Pondville Hosp., Walpole, Mass.
Cancer Res; 34(6):1319-1324 1974

Mammary tumorigenesis and mammary tumor transplantation immunogenicity were examined in breeding females of two syngeneic sublines of the C3H strain: in mammary tumor virus (MTV) plus nodule-inducing virus-infected C3H/Sed mice; and in MTV-free, nodule-inducing virus-infected C3Hf/Sed mice; and in explants of two separate MTV-free C3H/Ki hyperplastic alveolar nodule (HAN) outgrowth lines transplanted to the cleared mammary fat pads of syngeneic MTV-free C3Hf/Ki mice and transplanted to the cleared mammary fat pads of syngeneic MTV-infected C3H/Ki mice. Ninety-seven % of the C3H mice (29 of 30) developed mammary tumors at an average of 280 days. Of 43 different C3H tumors tested for transplantation immunogenicity in the C3H strain of origin, 13 (30%) had non-MTV-associated tumor-specific transplantation antigens (TSTA). All C3H tumors tested (20 of 20) for antigenicity in the C3Hf strain had MTV-associated transplantation antigens. Sixty-nine % of the C3Hf mice (34 of 49) developed mammary tumors at an average of 708 days. Of 16 different C3Hf tumors tested for antigenicity in the C3Hf strain of origin, 1 (6%) had TSTA. Tumor development in HAN line 1 was 44% at 297 days in C3Hf recipients and 100% at 175 days in C3H recipients. Tumor development in HAN line 2 was 75% at 225 days in C3Hf recipients and 87% at 142 days in C3H recipients. One of nine HAN line 1 tumors acquired TSTA during development in C3Hf/Ki mice, but none of 10 tumors acquired TSTA during development in C3H/Ki mice. One of 14 HAN line 2 tumors that arose in C3Hf/Ki mice acquired TSTA, compared with none of 15 tumors developing in C3H/Ki mice.

221. MAMMARY TUMOUR VIRUS (MTV)-SPECIFIC IMMUNE COMPLEX DEPOSITS IN RENAL GLOMERULI OF MTV-INFECTED TUMOUR-FREE MICE.

Zotter S, Lossnitzer A, Klahr G
Pathological Inst., Medical Acad. "Carl-Gustav-Carus," 8053 Dresden, East Germany
Acta Biol Med Ger; 35(2):253-257 1976

With the use of direct and indirect immunofluorescence tests, mammary tumor virus (MTV)-specific immune complex deposits were found in tumor-free female mice of the strains C3H/Bln, CBA/Bln, XVII/BlnfCBA/Bln, and CBA/BlnfXVII/Bln. These deposits consisted of immunoglobulin, complement, and MTV antigen(s). The immune complex deposition increased with age. Antibodies eluted from renal tissue homogenate reacted with both MTV-A and -B particles in immunofluorescence tests performed on mouse mammary tumor slices. The results confirm earlier findings of age-dependent spontaneously occurring anti-MTV antibodies in naturally infected mice. (36 refs)

222. SPONTANEOUS OCCURRENCE OF PRECIPITATING ANTIBODIES TO THE MAMMARY TUMOR VIRUS IN MICE.

Muller M, Hageman PC, Daams JH
Med. Acad. "Carl Gustav Carus", Dresden, Germany
J Natl Cancer Inst; 47(4):801-805 1971

Spontaneously occurring antibodies are reported in C3Hf and GR mice prenatally infected with Bittner mammary tumor virus (MTV-S) or GR virus (MTV-P), resp. The findings are at odds with previous reports that these mouse strains are tolerant to the MTV strains which they harbor. Multiparous female mice and sometimes mice stimulated by hypophysis grafting, with or without primary autochthonous mammary tumors, were of the following strains: C3H/HeA, CBA/BIN, GR, GRf, (C57BL x CBA/BrA)F1, BALB/c/DeA and (C3H x 020)F1 and (C3H x BALB/c)F1. Sera were tested in micro-Ouchterlony plates against purified MTV-S or MTV-P particles isolated from (C3H x 020)F1 or GR mammary tumors. Sera reacted with intact B particles and with ether-treated MTV-S, but never with nucleoid preparations of the virus. This suggested that the reaction was due to a virus-membrane antigen. Since most sera precipitating MTV-S also precipitated MTV-P, it was thought that both viruses had this membrane antigen. The finding of spontaneous antibodies precipitating MTV-S and MTV-P in GR and C3Hf mice was noteworthy, since it had not previously been possible to detect these antibodies in these strains. It was shown that no true tolerance exists to the outer membrane antigen in mice infected either neonatally (C3H and CBA) or prenatally (GR and C3Hf).

223. CHARACTERIZATION OF X/GF MICE WITH RESPECT TO THEIR RESISTANCE TO ONCOGENESIS.

Goldfeder A
Francis Delafield Hosp., New York, NY
Trans NY Acad Sci; 36(1):59-77 1974

A strain of mice designated X/Gf, inbred for the past 20 years by sister-brother matings, proved to have an extremely low susceptibility to the spontaneous development of neoplasms. Mice of this strain served as a model system in studies pertaining to the detection of endogenous characteristics that may be involved in resistance to neoplasia. The X/Gf mice produce high levels of antibodies against the mouse mammary tumor virus (MMTV), possess a high phagocytic activity and a high capacity to produce hemoantibodies, are resistant to polyoma virus, Friend leukemia virus (as adults), and to FBJ osteosarcoma virus, and exhibit low susceptibility to potent carcinogenic agents such as x-rays, urethan, 2-acetylaminofluorene, and 7,12-dimethylbenz(a)anthracene. No variants from those noted in other inbred mice were found either in the capacity for interferon production or in a representative number of isozymes. The low susceptibility of X/Gf mice to neoplastic transformation is attributed to their efficient immunological surveillance.

224. IMMUNOLOGICAL ASPECTS OF THE RELATIONSHIP BETWEEN HOST AND ONCOGENIC VIRUS IN THE MOUSE MAMMARY TUMOR SYSTEM.

Blair PB
Dept. Bacteriol., U. California, Berkeley
Isr J Med Sci; 7(1):161-186 1971

The immunological response to mammary tumor virus in the mouse is reviewed. Although the neonatally infected mouse is at least partially tolerant to the antigens of the virion and of the infected cells, both noninfected and infected animals are capable of responding immunologically to mammary tumor virus-associated antigenicity. There is some evidence that an infected female mouse which is genetically resistant to the virus may transmit resistance factors to her offspring, but genetically susceptible mice apparently do not produce such resistance factors. Protection against the development of challenge isografts can occur with adoptive transfer of lymphoid cells and transfer of serum antibody from immunized infected mice. Many attempts to immunize infected mice against mammary tumors have resulted, however, in acceleration of tumor growth rather than repression; since the dominant component in immunological protection against solid tissues containing foreign antigens is cell-associated and not humoral, the approach to immunotherapy should be concerned with evoking cell-associated immunological responses by immunization with membrane-bound antigens. An appropriate immunization with inactivated and similar but not identical virus strain might induce an immunologic response in the host which would be effective against its own virus-induced neoplasm.

225. IDENTIFICATION OF SPLENIC SUPPRESSOR CELL ACTIVITY IN MICE WITH MUMTV-INDUCED MAMMARY TUMORS (MEETING ABSTRACT).

Rudczynski AB, Mortensen RF
Dept of Biology, MIchigan Cancer Foundation, Detroit, MI 48201
Fed Proc; 36(3):1222 1977

Spleen lymphocytes from C3H and BALB/cfC3H mice bearing mammary tumor virus (MuMTV)-induced tumors displayed a lowered proliferative response to the T-cell mitogen, Concanavalin A (Con A), when compared to non-tumor bearing mice. Removal of adherent spleen cells on glass wool columns increased the response to Con A by 4-8 fold with spleen lymphocytes from mammary tumor bearing mice, but only two-fold or less with cells from control mice. Addition of unfractionated or glass-adherent spleen cells from tumor-bearing mice to cultures of syngeneic normal lymphocytes lowered their Con A responsiveness. The non-adherent cell populations from both tumor bearing and tumor free mice contained a slightly reduced fraction of membrane-Ig bearing lymphoid cells (56% vs 40%); however, there was no change in the proportion of theta-bearing cells or in the percentage of viable cells. The non-adherent spleen cell fraction contained a greatly reduced number of phagocytic cells, indicating that macrophages are a component of the suppressor cell population. These findings suggest that increased nonspecific suppressor cell activity may modulate the cellular immune response to murine mammary tumors. (Author Abstract)

226. NATURAL IMMUNITY IN THE ONCORNAVIRUS-INFECTED MOUSE.

Blair PB
Dept. Bacteriology and Immunology, Univ. California, Berkeley, CA 94720
Cancer Res; 36(2):734-738 1976

Immunological protection against oncornavirus-induced tumors with the virus introduced early in life was examined in BALB/cfC3H female mice infected neonatally with mammary tumor virus (MTV) and in BALB/c female mice supposedly free of MTV. Immune responses were assayed by the ability of spleen cells (with most of the macrophages removed) to act cytotoxically against target MTV-induced mammary tumor cells in a 2-day in vitro microcytotoxicity test and by the capacity of serum to block or enhance this activity. The neonatally MTV-infected mice possessed spleen cells capable of significant cytotoxicity activity against target MTV-induced mammary tumor cells in the microcytotoxicity assay. Spleen cells from the supposedly MTV-free mice also were specifically active as a result of horizontal antigen transmission. No quantitative differences existed between the reactivity of mice not susceptible to tumor development and those that may develop or have already developed tumors. There were,

however, qualitative differences between those at risk and those not at risk. Because of these differences, this type of assay may have prognostic potential.

227. ANTIBODY IN THE SERA OF TUMOR-BEARING MICE THAT MEDIATES SPLEEN CELL CYTOXICITY TOWARD THE AUTOLOGOUS TUMOR.

Blair PB, Lane MA, Mar P
Dept. Bacteriology and Immunology, Univ. California, Berkeley, CA 94720
J Immunol; 116(3):606-609 1976

Pretreatment of MTV-induced BALB/cfC3H mammary tumor cells with autologous serum caused increased spleen cell cytotoxic activity and the recruitment of previously inactive spleen cells to cytotoxic activity against the target cells. These recruiting antibodies were tumor-specific for individual tumors; pretreatment with such serum of target cells of an MTV-induced mammary tumor obtained from a different BALB/cfC3H female resulted in blocking of spleen cell activity. The autologous recruiting factors were active at dilutions of 1000 or more of whole serum and were found in the 19S fraction after gel filtration.

228. COMPLEXITY OF FACTORS IN SERA OF DIFFERENT MICE THAT AFFECT MTV-INDUCED MAMMARY TUMOR CELLS.

Blair PB, Lane MA, Mar P
Dept. Bacteriology and Immunology, Univ. California, Berkeley, CA 94720
J Immunol; 116(3):610-614 1976

Specific spleen cell activity in microcytotoxicity assay was altered by pretreatment of target mammary tumor virus (MTV)-induced mammary tumor cells with serum. Serum from both BALB/cfC3H females neonatally infected with MTV and BALB/c females horizontally exposed to MTV antigens blocked specific spleen cell activity against isologous mammary tumor cells. On fractionation of sera, blocking factors were localized in the 7S fraction. The 19S fraction contained recruiting factors that were not detectable in the unfractionated serum; these factors were active against isologous tumors and were thus distinct from the tumor-specific recruiting factors previously described in the sera of tumor-bearing females, which were active only against the autologous tumor. Antibodies mediating complement-dependent cell lysis were also detectable after serum fractionation.

229. BLOCKING OF SPLEEN CELL ACTIVITY AGAINST TARGET MAMMARY TUMOR CELLS BY VIRAL ANTIGENS.

Blair PB, Lane MA, Yagi MJ
Dept. of Bacteriology, Univ. of California, Berkeley, Calif. 94720
J Immunol; 151(1):190-194 1975

A series of microcytotoxicity tests were used to answer the questions of whether antigen alone is sufficient to inhibit spleen cell activity, and whether antigens of the mammary tumor virus (MTV) are effective in blocking spleen cell activity against mammary tumor cells. Virus preparations derived from the milk of six strains of mice and from culture fluids of the FUKU cell line were the source of antigen. Spleen cells from three types of donors were sources of immune cells. Cultures of MTV-induced BALB/cfC3H mammary tumors and a non-MTV-producing FUKU cell line served as sources of target cells. The donors consisted of two adult virgin BALB/cfC3H females, which made a T cell response to the tumor antigen; four multiparous but tumor-free BALB/cfC3H females, which made an even stronger T cell response, and a non-T cell response; and one adult virgin BALB/c female, whose response was entirely non-T cell. Three procedures were used for testing for blocking activity: (1) the target cells were treated with the antigen, (2) virus and spleen cells were added to target cells at the same time, and (3) the spleen cells were incubated with the antigen for 30 min before addition to the target cells. No blocking was observed by the first procedure; it was strongest by the third procedure. The T cell responses of the virgin and multiparous BALB/cfC3H females were effectively blocked, while non-T responses of multiparous BALB/cfC3H tumor-free females or of virgin BALB/c females were blocked by some, but not all, of the MTV antigen preparations. Murine leukemia virus (MuLV) was ineffective in blocking spleen cell activity against the MTV-induced mammary tumor cells. In comparable experiments involving the use of MuLV as the antigen, MuLV-producing FUKU cells as the target cells, and FUKU-sensitized lines as sources of spleen cells, the MuLV antigen was effective as a blocking agent, while MTV was not. The specificity of blocking demonstrates that it is immunologic in nature.

230. SERUM FACTORS IN MAMMARY NEOPLASIA: ENHANCEMENT AND ANTAGONISM OF SPLEEN CELL ACTIVITY IN VITRO DETECTED BY DIFFERENT METHODS OF SERUM FACTOR ASSAY.

Blair PB, Lane MA
Dept. Bacteriol. Immunol., Cancer Res. Lab., Univ. Calif., Berkeley, CA
J Immunol; 112(2):439-443 1974

Mammary tumors were induced by mammary tumor virus (MTV) in BALB/c mice to test the immune response to their own mammary neoplasms. Tumor cells for the immune assay were seeded in 20 microl RPMI medium and spleen cells from infected mice were added in a ratio of 100:1 spleen to tumor cells and incubated for 48 hr then washed, fixed, stained and counted. Lymphocytes from spleens were obtained by lysing the RBC and incubating to allow macrophages to settle out. The remaining suspension of spleen cells were counted and then added to target tumor cells. Control spleen cells were obtained from healthy BALB/c females. Serum samples were inactivated by heating, diluted (1:4), filtered and frozen; samples were pooled from several mice and tested in three ways: 1) with lymphocytes by suspension of spleen cells in serum, the suspension was incubated for 30 min, diluted, resuspended and added to target tumor cells; 2) with tumor cells, the medium of tumor cells was replaced with diluted serum, incubated for 30 min, drained and spleen cells added; and 3) serum and spleen cells were mixed prior to the addition to target cells. The addition of spleen cells decreased tumor cell survival, compared to control tumor cell cultures. Pretreatment of spleen cells with sera resulted in a partial blocking of the effect of spleen cells on tumor cell survival. Treatment of spleen cells with control serum from healthy mice did not affect the activity of spleen cells to lower tumor cell survival. Regardless of whether the second or third treatment of serum was utilized, whenever serum from a tumor donor, other than the donor of tumor cells was tested, complete blocking of the effect of spleen cells on tumor cells was seen. When tumor cells and serum were obtained from the same mouse, addition of serum to tumor cells by method two or three resulted in no blocking of spleen cell activity. Survival of tumor cells was less than in the presence of spleen cells alone. The source of spleen cells was not important. (13 refs)

231. IN VITRO DETECTION OF IMMUNE RESPONSES TO MTV-INDUCED MAMMARY TUMORS: ACTIVITY OF SPLEEN CELL PREPARATIONS FROM BOTH MTV-FREE AND MTV-INFECTED MICE.

Blair PB, Lane MA, Yagi MJ
Dept. Bacteriol. Immunol., Cancer Res. Lab., Univ. Calif., Berkeley, CA
J Immunol; 112(2):693-705 1974

Spleen cell preparations from groups of 5.5-8 mo-old multiparous BALB/cfC3H mammary tumor virus (MTV)-induced mammary tumor donors showed significant activity against their own tumor cells (survival percentages, 45-77% of control values). Controls consisted of mice bearing D1-DMBA-3 and D1-DMBA-4 induced mammary tumors. Tumor donor spleen cells were significantly active against other MTV-induced mammary tumor cells (survival 45-71% of control). Spleen cells from multiparous BALB/cfC3H tumor donors were inactive against MTV-free, carcinogen-induced mammary tumor cells. Spleen cells from normal virgin MTV-infected, 8-32-wk-old BALB/cfC3H mice were active against MTV-induced mammary tumor cells (74-97% survival relative to control), while cells from 8-13 wk-old MTV-free mice were inactive except in 2 cases. Cells from 14-30 wk-old virgin female MTV-free BALB/cfC3H mice were active against mammary tumor cells (40-80% survival), as were cells from 28 wk-old BALB/c male mice (66-72% survival). Prior addition of serum from normal BALB/c mice before addition of spleen cells from tumor donors partially blocked the action of spleen cells from normal adult BALB/c females only. Pretreatment of MTV-induced mammary tumor cells with BALB/cfC3H serum blocked completely the action of spleen cells from tumor donors and normal BALB/cfC3H female mice. Results indicate that during the first mo of life, MTV-free females are exposed to antigens later found on MTV-induced mammary tumors. (21 refs)

232. VIRUS-DEPENDENT CYTOSTATIC ACTIVITY TO MAMMARY TUMOR CELLS OF LYMPHOCYTES FROM NORMAL MICE.

Gillette RW, Lowery LT
Meloy Laboratories, Inc., Springfield, Virginia 22151
Cancer Res; 36(11):4008-4014 1976

A cytostasis assay has been used to study the natural immunity of mice to murine mammary tumor virus (MTV). Spleen cells from adults of all strains tested were found to be cytostatic to a variety of MTV-positive mammary tumor cell lines. Newborn spleen cells were unreactive in the same cytostasis assay. The degree of reactivity to the target cells was greater in spleen cell preparations from low MTV expressors than from syngeneic, high MTV expressors. The cytostasis was specific, since MTV antigens prepared from gradient-purified whole MT virions significantly blocked the reaction. In addition, spleen cells were totally nonreactive to MTV-negative cell lines. Other types of lymphoid cells, such as lymph node cells as well as peritoneal macrophages, were highly cytostatic under similar conditions. Spleen cells from nude athymic donors were not cytostatic. Since depletion of splenic T-lymphocytes by use of anti-theta serum also did not significantly affect cytostasis, it was concluded that T-cells were required for initiation of immunity to MTV but that the effector cells were not theta positive. Blocking factors were found to exist in the sera of mammary tumor-bearing animals that prevented cytostasis by reactive spleen cells. (Author Abstract)

233. CHARACTERIZATION OF CYTOTOXIC EFFECTOR CELLS IN THE MOUSE MAMMARY TUMOR SYSTEM.

Lane MA, Roubinian J, Slomich M, Trefts P, Blair PB
Dept. Bacteriol. Immunol., Univ. California, Berkeley
J Immunol; 114(1):24-29 1975

Cell types involved in the in vitro immune response to murine mammary tumor virus (MTV)-induced BALB/cfC3H mammary tumors were studied using techniques designed to inactivate or deplete different cytotoxic effector cells from spleen cell populations. The minimal activity of spleen cells from neonatally MTV-infected virgin BALB/cfC3H females was dependent upon the presence of T cells. Spleens from multiparous BALB/cfC3H females had a more active T cell population and, in addition, a non-T cell population which was active early in the culture period. The responses of spleen cells from multiparous BALB/cfC3H females bearing small mammary tumors were similar to those of spleen cells from tumor-free multiparous females. However, after the tumors had grown to a large size, the activity of the non-T cell population was no longer detectable. The cytotoxic activity of spleen cells from BALB/c females older than 14 weeks (supposedly not infected with MTV) was not dependent upon the presence of T cells. No activity was shown by spleen cells from BALB/c females younger than 14 weeks. Positive control spleen cells were obtained from C3H female mice who had been immunized against BALB/c histocompatibility antigens by a skin allograft; both a T cell and a non-T cell response were found. The results suggest that the non-T cell response as well as the T-cell response may be important in the host's rejection of foreign tissue. In the T cell cytotoxic response, the specificity appears to lie in the recognition by T cells of specific antigens on the surface of the tumor target cells. B cells may supply small amounts of antibody which is specific for antigen on the mammary tumor target cells, this specific antibody mediating non-T cell cytotoxicity.

234. MOUSE MAMMARY TUMORIGENESIS BY MAMMARY TUMOR VIRUS IN THE ABSENCE OF THYMUS, SPLEEN OR BOTH ORGANS.

Squartini F
Med. Sch., U. Pisa, Italy
Isr J Med Sci; 7(1):26-35 1971

Mice of various strains underwent thymectomy at 1 day-of-age or splenectomy at 2 days-of-age, or both operations; all the mice strains used except one carried a spontaneous infection with mammary tumor virus (MTV). In a group of female BALB/c (MTV-free) mice injected with MTV after undergoing thymectomy, 39% of animals developed hyperplastic alveolar mammary nodules, whereas the percentage of intact mice developing nodules in groups given MTV was 100%; the percentage of intact mice developing nodules in groups not given MTV was 20%. The incidence of pregnancy-dependent mammary tumors or plaques was observed in BALB/cf(RIII) MTV-infected mice; in intact mice, mammary tumors were pregnancy-dependent to some degree in 81.5% of the cases, whereas in thymectomized mice, tumors were partially pregnancy-dependent in only 23% of the cases. In intact BALB/cf(C3H) mice frank mammary tumors developed in 82% of cases, whereas thymectomized mice of the same strain developed lesions in 46% of cases. Thymectomy also prolonged the latent period for the appearance of these tumors. In force-bred mice the incidence of mammary tumor development was similar to that in intact mice. Thymectomy did not affect the frequency of mammary tumors in RIII strain mice. In splenectomized BALB/cf(C3H) mice, the incidence and latency of mammary tumor development was reduced; tumors developed in 82% of intact mice and in 52% of splenectomized mice. In mice of this strain which underwent

both thymectomy and splenectomy, splenectomy partially suppressed the depressive effect of thymectomy on tumor development; splenectomized and thymectomized mice had tumor incidence patterns similar to those seen in intact mice. Splenectomy did not affect tumor incidence in RIII strain mice.

235. MAMMARY TUMORIGENESIS IN SPLENECTOMIZED MICE.

Squartini F, Bolis GB
U. Pisa Med. Sch., Italy
Tex Rep Biol Med; 28(1-2):115-121 1970

Female mice of BALB/cf(C3H) and RIII strains were subjected to splenectomy, thymectomy, both operations, or no operation to investigate the effect of splenectomy on mammary tumorigenesis in mice carrying spontaneous mammary tumor virus infection. In BALB/cf(C3H) females, neonatal splenectomy decreased both the incidence and age of onset of mammary tumors from 82% to 52%, and by an average of 102 days, resp. Thymectomy decreased the incidence of mammary tumors (46%) and increased the age of onset by an average of 130 days; splenectomy of previously thymectomized females partially suppressed the effect of thymectomy and restored the pattern of tumor development to that seen in intact controls. No significant effect was noted on mammary tumorigenesis in RIII mice undergoing splenectomy alone or associated with thymectomy.

236. MOUSE STRAIN AND BREEDING STIMULATION AS FACTORS INFLUENCING THE EFFECT OF THYMECTOMY ON MAMMARY TUMORIGENESIS.

Squartini F, Olivi M, Bolis GB
Med. Sch. Pisa, Italy
Cancer Res; 30(7):2069-2072 1970

Thymectomies were performed on newborn BALB/cf(C3H), BALB/cf(RIII), and RIII strain mice which carried spontaneous mammary tumor virus infection to determine the effect of this operation on tumorigenesis. In BALB/cf(C3H) virgin females, thymectomy decreased mammary tumor incidence from 82 to 46% and delayed tumor onset by about 5 months; in BALB/cf(RIII) force-bred females, thymectomy delayed tumor onset by about 2 months but did not significantly affect the final mammary tumor incidence. In RIII females, either virgins or breeders (normal and force-bred), thymectomy had no effect on frequency and onset of mammary tumors. Mouse strain and breeding condition does appear to influence the effect of thymectomy and the immunological responsiveness of the host animal to virus induced tumorigenesis.

237. THE ROLE OF T AND SUPPRESSOR CELLS IN MTV-DIRECTED CELLULAR IMMUNITY.

Creemers P, Bentvelzen P
Radiobiological Inst TNO, Rijswijk, The Netherlands
Eur J Cancer; 13(3):261-267 1977

The lymphocyte population from mice immunized with mammary tumour virus (MTV) which responds in vitro with blastogenesis in the presence of MTV, proves to be T cells. In mice bearing spontaneous MTV-induced mammary tumours, this T cell reactivity was very often depressed. The depression was partly due to the presence of suppressor cells which have adherent properties. These suppressor cells appear early during tumour growth and exert their greatest influence when the tumour weighs 0.5-1.5 g. In animals bearing larger tumours less suppressor cells were present and the hyporeactivity in the lymphocyte stimulation test must also be due to other factors. (10 Refs) (Author Abstract)

D. Alteration of Immunity to MuMTV and MuMTV-Induced Tumors

238. IMMUNOTHERAPY OF CANCER WITH ANTIBODY.

Shin HS, Pasternack GR, Economou JS, Johnson RJ, Hayden ML
Dept. Microbiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205
Science; 194(4262):327-329 1976

The immunotherapy of a syngeneic solid tumor transplanted im in C3H/HeN MTV mice with an antibody raised in mice immunized with an attenuated tissue culture line of tumor cells is reported. The in vivo doubling time of the tumor was 18 hr, and tritiated thymidine labeling studies indicated a lag period of less than 3 hr. Mice inoculated with 3 x 10^5 tumor cells were treated with a constant amount of antibody at various times thereafter. All mice treated with antibody up to day 2 did not develop tumors. In the group treated on day 5, only one mouse of five failed to develop a tumor, and when treatment was carried out after day 5, all mice developed tumors. An increase in the tumor cell number was identified as the sole reason for the observed increasing resistance with time after tumor inoculation, since the susceptibilities of resident tumors and a comparable number of freshly injected tumors were similar. Transient cytostasis was ruled out as a significant cause in the antibody-mediated suppression of tumor growth, since mice which did not develop tumors by day 22 continued to be tumor-free throughout the period of observation (180 days). Problems associated with clinical application of this type of immunotherapy include the possibility of weakening the host's immunity and the shortage of effector cells. (11 refs)

239. REJECTION OF SYNGENEIC MAMMARY TUMOR CELLS FOLLOWING IMMUNIZATION WITH KILLED MOUSE MAMMARY TUMOR VIRUS (MUMTV).

Charney J, Moore DH, Holben JA, Cody CM
Inst. Med. Res., Camden, N. J.
Fed Proc; 33(3,Part1):782 1974

240. IMMUNOTHERAPEUTIC STUDIES IN MICE WITH THE METHANOL-EXTRACTION RESIDUE (MER) FRACTION OF BCG: SOLID TUMORS.

Yron I, Weiss DW, Robinson E, Cohen D, Adelberg MG, Mekori T
Lautenberg Cent. Gen. Tumor Immunol., Hadassah Med. Sch., Jerusalem, Israel
Natl Cancer Inst Monogr; 39:33-55 1973

The therapeutic efficacy of the methanol-extraction residue (MER) fraction of inactivated BCG organisms against solid tumors (carcinogen-induced fibrosarcomas, and mammary tumor virus-negative and positive, mammary sarcomas) is described. The residue was admin alone or in combination with x-irradiation and chemotherapy (cyclophosphamide, 5-fluorouracil, vinblastine sulfate, methotrexate, and thio-TEPA). The underlying assumption is that the ability of MER to heighten resistance against neoplastic cells is due to a nonspecific stimulation of immunologic reactivity against tumor-associated cell surface antigens. (25 refs)

241. EFFECT OF TREATMENT WITH THE MER TUBERCLE BACILLI FRACTION ON THE SURVIVAL OF MICE CARRYING MAMMARY TUMOUR ISOGRAFTS: INJECTION OF MER AT THE TUMOUR SITE OR AT A DISTAL LOCATION.

Cohen D, Yron I, Haber M, Robinson E, Weiss DW
Lautenberg Center General Tumour Immunology
Hadassah Medical Sch., Jerusalem, Israel
Br J Cancer; 32(4):483-490 1975

The methanol extraction residue (MER) of tubercle bacilli were used alone or with irradiation in the treatment of BALB/c mice carrying either of two syngeneic mammary tumors (D7T4S or MTV). Radiotherapy consisted of 2,000 rads for D7T4S and 3,000 rads for MTV. MER treatment consisted of either a single 0.4 ml s.c inj s.c at a distal site (contralateral leg) or two simultaneous inj of 0.2 ml, one at a distal site and the other into the tumor area. Treatments were given on d. 17 or 21 after tumor implantation. Mice receiving MER directly into the tumor area as well as elsewhere were afforded no protection, where MER alone distally provided significant survival protection both in comparison with saline controls and with animals given MER into the tumor area. There were no cures. In some experiments, MER admin into the tumor area as well as elsewhere caused earlier deaths than in control groups. Irradiation on d. 17 prolonged survival, and combination of radiation on d. 17 with MER on d. 21 was superior in terms of survival only when MER was admin at a site distal to the tumor. When MER was admin on d. 17 followed by radiation on d. 21, radiation alone improved survival over controls, as did combined treatment regardless of the site of MER treatment, and in this experiment, inj of MER into the tumor area as well as elsewhere was slightly more efficacious than distal admin of MER alone. Nor did MER admin distally improve the results of irradiation alone. (16 refs)

242. ACCELERATED DEVELOPMENT OF TRANSPLANTED MAMMARY TUMORS IN MICE PRETREATED WITH THE METHANOL EXTRACTION RESIDUE OF BCG AND PREVENTION OF ACCELERATION BY CONCOMITANT SPECIFIC IMMUNIZATION.

Jacobs DM, Kripke ML
Dept. Biol., U. California, San Diego, La Jolla
J Natl Cancer Inst; 52(1):219-224 1974

Pretreatment of BALB/cfc3H mice with the methanol extraction residue (MER, two 0.5 mg injections ip) of Bacillus Calmette Guerin 14 and 3 days before challenge with syngeneic MTV+ mammary tumors (1 mm3 sc) resulted in an increased incidence of tumors compared with that in the saline-treated controls. When the animals were treated with MER several weeks before tumor challenge, tumor development was also accelerated. Faster tumor development did not seem related to the immunogenicity of these tumors, since acceleration was noted in syngeneic BALB/cfC3H (MTV+) mice in which these tumors were not detectably immunogenic, and also in syngeneic BALB/c (MTV-) hosts in which the tumors were strongly immunogenic. When MER treatment of either MTV+ or MTV- hosts was combined with specific tumor immunization, more rapid development of the challenge tumors did not occur, but there appeared to be not added beneficial effect of the combined treatment over immunization alone.

243. ACTIVE SPECIFIC IMMUNOTHERAPY OF CANCER IN EXPERIMENTAL ANIMALS. (PP. 227-244)

Simmons RL, Rios A
Host Defense Against Cancer and Its Potential Proceedings of the 5th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975. Mizuno D, Chihara G, Fukuoka F, Yamamoto T, Yamamura Y, ed. Baltimore, Univ Park Press, 1975.

The immunoregression of transplantable and spontaneous mammary tumors in mice was studied to determine whether it could be induced by challenge with Vibrio cholerae neuraminidase (VCN)-treated tumor cells. Firmly established transplantable C3H/HeJ mammary carcinomas were inhibited by host (C3H/HeJ and C3HeB/FeJ mice) challenge with VCN-treated tumor cells. The effect was totally immunospecific; even VCN-treated tumors bearing shared mammary tumor virus (MTV) antigen could not induce the regression. Thus, VCN was capable of increasing the immunogenicity of the private, unique-unshared tumor antigens on mammary carcinomas, but was incapable of increasing the immunogenicity of the shared MTV-associated tumor antigen even in syngeneic C3HeB/FeJ MTV-free mice. The immunoregressive effect of VCN-treated tumor cells could be augmented by subtotal or total surgical excision of large transplantable tumors. Spontaneous mammary tumors in retired breeder C3H/HeJ female mice were made to regress by repeated intratumor injections of VCN and/or BCG and by total excision and immunotherapy with VCN-treated autochthonous mammary tumor cells. The use of VCN-treated transplantable mammary tumor cells sharing the MTV-associated antigen was not better than excision alone. The evidence indicates that active specific immunotherapy of spontaneous tumors with VCN-altered tumor cells may require the use of autochthonous cells.

244. ACTIVE SPECIFIC IMMUNOTHERAPY WITH MODIFIED TUMOR CELLS.

Simmons RL, Rios A
Dept. Surg., Univ. Minnesota, Minneapolis
Immunological Aspects of Neoplasia: Twenty-Sixth Annual Symposium on Fundamental Cancer Research 1973; (Williams and Wilkins Co, Baltimore):513-526 1975

Experiments are described that demonstrate regression of spontaneous and transplanted tumors in mice following inj of Vibrio cholerae neuraminidase (VCN) and bacillus Calmette-Guerin (BCG). Inocn. (s.c) of female C3H/HeJ mice with 2 x 10^4 viable methylcholanthrene-induced fibrosarcoma (MC-42) tumor cells pretreated with VCN or heat-inactivated VCN (25 units/ml/10^6 cells) plus mitomycin C (25 ug/ml/10^6 cells) prevented growth of MC-42 tumors implanted 10-20 d earlier (2 x 10^5 cells s.c) in 26 of 30 animals. Similarly, VCN-treated tumor cells (10^6 viable cells s.c) caused regression of firmly established tumors (2 x 10^4 cells s.c), while heat-inactivated VCN had no effect on the growth of the initial inoculum. MC-42 tumors also did not regress when challenged with VCN-treated MC-43 tumor cells. Combined s.c admin of 1 mg BCG plus 10^6 VCN-treated MC-42 tumor cells (in six doses on alternate d beginning 15 d after tumor inocn) caused total regression in 24 of 42 cases, compared with 6/17 when BCG was omitted. Intralesional inj of 50 units of VCN also inhibited tumor growth, causing total regression in 4/12 instances. In the case of spontaneously-arising mammary carcinomas, inj of tumor masses (0.7-1.0 cm diameter) with 50 units of VCN and 1 mg BCG every 4 d resulted in total disappearance of 4/13 tumors. Secondary tumors developed in 9/13 animals receiving VCN 1 BCG and 2/10 given inactivated VCN 1 BCG, but growth was generally inhibited by repeated local inj. Immunospecific regression of mammary tumors was induced even in mice dying of immunodistinct tumors inoc

contralaterally, as shown in both C3H/HeJ mice (neonatally infected with mammary tumor virus) and C3HeB/FeJ mice (virus free) inoc in opposite flanks with M-1 and M-2 tumor cells (4 x 10^4 each) and subsequently given six challenging s.c inj of VCN-treated M-1 or M-2 tumor cells. These results demonstrated that VCN could augment the immunogenicity of private tumor antigens but not that of the stronger mammary tumor virus antigen. (37 refs)

245. EXPERIMENTAL CANCER IMMUNOTHERAPY: MODIFICATION OF TUMOR CELLS TO INCREASE IMMUNOGENICITY.

Rios A, Simmons RL
Dept. Surgery, Univ. Minnesota, Minneapolis, MN 55455
Ann NY Acad Sci; 276:45-60 1976

Experiments to determine whether the immunoregression of transplantable and spontaneous mammary tumors can be induced by challenge with tumor cells treated with Vibrio cholerae neuraminidase (VCN) are described. Firmly established transplantable C3H/HeJ mammary carcinomas were inhibited by host challenge with VCN-treated tumor cells (25 units VCN/ml/10^6 cells) when recipient syngeneic C3H/HeJ female recipient mice were given intratumor injections of 10^6 tumor cells incubated with VCN 15 days after the sc injection of 40,000 transplantable mammary adenocarcinoma cells. The effect was totally immunospecific, and even VCN-treated tumors bearing shared mammary tumor virus (MTV) antigen could not induce the regression. Thus, VCN was capable of increasing the immunogenicity of the private, unique-unshared tumor antigens on mammary carcinoma but was not capable of increasing the immunogenicity of shared MTV-associated tumor antigen even in syngeneic C3HeB/FeJ MTV-free mice. The immunoregressive effect of VCN-treated tumor cells was augmented by subtotal or total surgical excision of large transplantable tumors. Spontaneous mammary tumors in retired breeder C3H/HeJ female mice were made to regress by either repeated intratumor injections of VCN (50 units) and/or BCG (1 mg) or total excision and immunotherapy with VCN-treated autochthonous mammary tumor cells. The use of VCN-treated transplantable mammary tumor cells sharing the MTV-associated antigen was not better than excision alone. The evidence supports the idea that active specific immunotherapy of spontaneous tumors with VCN-altered tumor cells may require the use of autochthonous cells. (44 refs)

246. MODIFIED TUMOR CELLS IN THE IMMUNOTHERAPY OF SOLID MAMMARY TUMORS.

Simmons RL, Rios A, Trites P
Mayo Memorial Building-Box 185, Univ. Minnesota, Minneapolis, MN 55455
Med Clin North Am; 60(3):551-565 1976

Studies on the immunoregression of transplantable (M-1 and M-2) and spontaneous mammary tumors by Vibrio cholera neuraminidase (VCN)-treated tumor cells are reported. Injection of 10^6 VCN-treated M-1 cells in the contralateral flank resulted in marked reduction of tumor growth rate and in total regression of 4/40 tumors in C3H/HeJ mice carrying sc M-1 tumor, but heat-inactivated VCN-treated M-1 cells and VCN-treated M-2 cells were ineffective. Cross-immunization experiments strongly suggested that M-1 and M-2 tumors share the same mammary tumor virus antigen, and that C3H3B/FeJ mice can be immunized by the mammary tumor virus antigen from the C3H/HeJ mammary tumors. Separate M-1 and M-2 tumors were established sc in opposite flanks of C3H/HeJ mice (which are infected with mammary tumor virus) and C3HeB/FeJ mice (which do not carry mammary tumor virus): VCN-treated M-1 or M-2 cells were injected at a third site. Growth inhibition and regression of firmly established M-1 tumors took place only on animals challenged with VCN-treated M-1 cells, but not with heat-inactivated VCN-treated M-1 cells or VCN-treated M-2 cells. M-2 tumors did not regress if mice were challenged with M-2 cells exposed to heat-inactivated VCN-treated M-2 cells or with VCN-treated M-1 cells, but VCN-treated M-2 cells did result in inhibition of the growth of M-2 tumors. Wedge excision of M-2 tumors on day 15 added nothing to the immunoregressive effect of VCN-treated M-2 cells, but when treatment was delayed until day 25, tumor regrowth was significantly inhibited by a combination of partial, subtotal, or attempted total excision plus challenge with VCN-treated tumor cells. Seven of 10 animals were cured by attempted total tumor excision plus VCN-treated tumor cells. Intratumoral injection of VCN (50 units) or BCG (1 mg) significantly slowed growth, caused tumor regression, and prolonged life of animals carrying spontaneous mammary adenocarcinomas, but a combination of VCN and BCG intralesionally was much more effective. Among C3H/HeJ mice with spontaneous mammary tumors, total excision with a narrow margin on day 14 of tumor growth cured 7/15 and significantly prolonged life. Local treatment with VCN M-1 cells did not alter the effect of total excision alone, but mice treated with total excision and VCN-treated autochthonous tumor cells had a significantly improved survival. (43 refs)

247. REGRESSION OF SPONTANEOUS MAMMARY CARCINOMAS USING DIRECT INJECTIONS OF NEURAMINIDASE AND BCG.

Simmons RL, Rios A, Kersey JH
Dept. Surg., Univ. Minn., Minneapolis
J Surg Res; 12(2):57-61 1972

Spontaneous mammary adenocarcinomas in adult (9-15 mo) female C3H/HeJ mice naturally infected with mammary tumor virus were inj every 4th d with 0.1 ml of soln containing Medium 199, Vibrio cholerae neuraminidase (VCN; 50 units), heat-inactivated VCN (IVCN), Mycobacterium bovis (strain BCG; 1 mg), or a combination of VCN, IVCN, and/or BCG. Tumor growth was significantly slowed and animal life prolonged with BCG (79.5 d) and VCN (88 d), as compared with Medium 199 (66 d) and IVCN (60 d). VCN combined with BCG led to tumor regression (4/13 tumors disappeared) and prolonged life (107 d). By analogy with the effect of these agents in syngeneic transplanted tumors, the effect can be considered immunological. Growth of 2nd adenocarcinomas, common in mice treated with VCN and/or BCG and related to regression of the first tumor, may possibly mean the immunity induced is directed not to the mammary tumor virus antigen but to the weaker specific antigens on the treated tumor. (22 refs)

248. FURTHER IMMUNIZATION STUDIES WITH MAMMARY TUMOR VIRUS.

Charney J, Holben JA, Cody CM, Moore DH
Inst. Medical Res., Camden, NJ 08103
Cancer Res; 36(2):777-780 1976

The protection of young C57BL mice, substrains RIIIf and Af, against future viral challenge by an im inoculation with formalin-inactivated murine mammary tumor virus in Freund's complete adjuvant was studied. A single im dose of virus greatly reduced viral expression and mammary tumorigenesis in Af (tumor incidence, 39%) and RIIIf (tumor incidence, 11%) mice, which carry only endogenous, gamete-transmitted virus. In C57BL mice, 1 ug of vaccine in Freund's complete adjuvant protected against later challenge with RIII virus.

249. EFFECT OF TRANSIENT IMMUNOSUPPRESSION ON HOST RESPONSE TO NEONATALLY INTRODUCED ONCOGENIC VIRUS.

Blair PB

Cancer Res. Genet. Lab., U. California, Berkeley

Cancer Res; 32(2):356-359 1972

BALB/c female mice, which normally lack mammary tumor virus (MTV) were given immunosuppressive injections of either antithymocyte serum (ATS) or normal rabbit serum (NRS); C3H female mice, which normally carry MTV were given globulin preparations of ATS (ATG) or globulin preparations of NRS (NRG). Some mice given the immunosuppressive treatments were inoculated with isogenic mammary tumor cells to test cell-mediated immune reactivity of serum. In C3H mice not given tumor inocula, none of those given NRG developed circulating anti-MTV antibodies in serum; 62% of C3H mice given ATG but no tumor cells developed serum antibodies. Both NRG- and ATG-treated C3H mice inoculated with mammary tumor cells showed serum anti-MTV antibody. More ATG-treated mice than NRG-treated mice developed antibody (83 vs 38%). In BALB/c mice, anti-MTV antibodies appeared earlier in ATS-treated than in NRS-treated animals.

250. EFFECT OF IMMUNE MANIPULATION ON NATURAL IMMUNE RESPONSES TO MURINE MAMMARY TUMOR ANTIGENS.

Blair PB, Lane MA

Dept. Bacteriology and Immunology, Cancer Res. Lab., Univ. California, Berkeley, CA 94720

J Natl Cancer Inst; 59(1):251-257 1977

The virus-host-relationship in BALB/c/C3H virgin female mice neonatally infected with an oncogenic virus (mammary tumor virus) (MuMTV) was significantly altered by a brief immunosuppressive treatment during young adult life. Natural immune responses were augmented and changed. The ability of lymphoid cells to attack target cells expressing MuMTV-associated antigens was significantly increased, and a new component, a non-T-cell reactivity, was added to the T-cell reactivity found in normal females. Serum blocking factors were both quantitatively and qualitatively altered. (Author abstract) (15 Refs)

251. INFLUENCE OF PARABIOSIS ON TUMOUR GROWTH IN TUMOUR BEARING ANIMALS.

Postuma HS

Lab. Exp. Surg., U. Amsterdam, The Netherlands

Arch Chir Neerl; 15(3):267-282 1973

The effect of parabiosis, or cross-circulation, on the growth of a transplanted mammary carcinoma originally induced in the C57 black strain by mammary tumor virus was studied in 150 experiments on highly inbred female F1 hybrid mice crossing C57 black and CBA strains. Tumor growth was significantly retarded if cross-circulation was made 3 days before grafting or 3 and 6 days after grafting. Parabiosis 9 days after grafting had no retarding effect. When parabiosis was made between tumor bearing animals and immune animals obtained by separation of the anastomosis 14 days after parabiosis with a tumor bearing animal, a significant influence on tumor growth was observed. Immunodiffusion and immunofluorescence showed the presence of humoral tumor specific antibodies in the tumor-host-system. It is concluded that parabiosis is a valuable technique for demonstrating and studying the specific immunological anti-tumor activity of the host after actively growing tumors have been implanted.

252. DIFFERENTIAL RESPONSE OF TUMOR BEARER AND NORMAL MOUSE SPLEEN CELLS TO PHA AND SYNGENEIC TUMOR EXTRACTS IN VITRO: EFFECT OF XENOGENEIC AND SYNGENEIC SERA (MEETING ABSTRACT).

Laing CA

Mt Sinai Sch of Medicine, New York, NY 10029

Fed Proc; 35(3):387 1976

Reactivity of spleen cells from (tumor MTV-induced) bearing BALB/c and normal BALB/c mice to PHA and a Perchloric acid extract (EMT) of mammary tumor was measured by the uptake of ^{3}H-thymidine in vitro, in the presence of human AB plasma (ABP) and normal BALB/c sera (NBS). Stimulation indexes (SI) (cpm in stimulated cultures/cpm in serum control) were as follows: normal cells + ABP (SI)PHA 696, (SI)EMT 32.8; tumor bearer cells + ABP (SI)PHA 157, (SI)EMT 5.6; normal cells + NBS (SI)PHA 1.7, (SI)EMT 2.0; tumor bearer cells + NBS (SI)PHA 17 (SI) EMT 177. Whereas in ABP the PHA response in normal cells is 4 x that in tumor bearer cells; in NBS the response in tumor bearer cells is 100 x that in normal cells. Tumor bearer cells respond to EMT with more dramatic effect in NBS than in ABP. ABP promotes the response of normal syngeneic spleen cells to EMT. The conclusions from these findings are: PHA responsive cells are either more numerous or more sensitive in tumor bearer than in normal mice in a syngeneic system; the high responsiveness of normal cells to PHA in xenogeneic compared to syngeneic sera may be due to promoting factors in xenogeneic sera rather than inhibitory factors in syngeneic sera; PHA and EMT might have stimulated similar cell populations; and since tumor bearer animals are infected with the MTV and EMT contains MTV related antigens, possible viral influence on both responses cannot be ruled out. (Author Abstract)

253. DIFFERENTIAL EFFECT OF NEURAMINIDASE ON THE IMMUNOGENICITY OF VIRAL ASSOCIATED AND PRIVATE ANTIGENS OF MAMMARY CARCINOMAS.

Simmons RL, Rios A

Dept. Surg., Univ. Minn., Minneapolis

J Immunol; 111(6):1820-1825 1973

The inhibition of firmly established transplantable C3H/HeJ mammary carcinomas by host challenge with Vibrio cholerae neuraminidase (VCN)-treated tumor cells was studied with 2 tumors (M1 and M2) in C3H/HeJ mice, which were infected with mammary tumor virus, and in C3HeB/FeJ mice, believed not to harbor the virus. Both tumors resulted in immunity in both strains of mice, but inj of spleen cells from each line did not result in tumor immunity in the other. In mice of both strains carrying M1 tumor, sc inj of VCN-treated M1 cells caused regression in 5-17% of mice and a significant reduction in tumor diameter and an ILS in the other animals. No effect was noted when heat-inactivated VCN-treated M1 cells were used or when VCN-treated M2 cells were used. When animals of each strain carrying well established M1 and M2 tumors simultaneously (1 in each flank) were challenged at a 3rd site with either VCN-treated M1 or VCN-treated M2 cells, again both strains reacted similarly: only M1 tumors regressed (and mean tumor size was markedly reduced in remaining M1 tumors) when VCN-treated M1 cells were inj, and only M2 tumors regressed (and remaining M2 tumors shrank) following VCN-treated M2 cells. Thus, even viral-free mice failed to reject M1 tumors when challenged with VCN-treated M2 cells and vice versa. The effect was totally immunospecific, even VCN-treated tumors bearing shared mammary tumor virus antigen being unable to induce regression. Thus, VCN is capable of increasing the immunogenicity of the private, unique unshared tumor antigens on mammary

carcinomas; VCN is incapable of increasing the immunogenicity of the shared mammary tumor virus associated tumor antigen. (35 refs)

254. CELL LINE-SPECIFIC CELL SURFACE COMPONENTS OF HYPOTETRAPLOID ASCITES MAMMARY CARCINOMA CELLS INDUCING HUMORAL REACTIONS IN THE SYNGENEIC HOST.

Tanino T, Saito M, Egawa K
Department of Cell Chemistry, Institute of Medical Science, University of Tokyo, Shiroganedai, Minatoku, Tokyo 108, Japan
Int J Cancer; 17(6):736-741 1976

Cell-line-specific cell surface components were demonstrated on cells of various hypotetraploid ascites cell lines, but not on hyperdiploid cells derived from a mammary carcinoma induced by mammary tumor virus (MTV) in syngeneic C3H/He mice. These substances caused cell-line-specific transplantation antigenicity and were identified, together with MTV-associated substances and tumor-associated embryonic materials, as being the binding sites for tumor cell agglutinating factors found in sera from tumor-bearing and regressor animals. Particles containing the cell-line-specific substances were released from these cells by hypotonic treatment. They could be purified as a single peak in a sucrose density gradient. They were, however, not dissociated from the MTV-associated substances. Absorption studies of agglutination activity were extensively used for demonstration of specificity. (Author Abstract)

255. HUMORAL REACTIONS IN SYNGENEIC HOSTS AGAINST TUMOR CELL SURFACE INCOMPLETE SACCHARIDE MOIETIES.

Tanino T, Egawa K
Dept. Cell Chemistry, Inst. Medical Science, Univ. Tokyo, Shiroganedai, Minatoku, Tokyo 108, Japan
Int J Cancer; 17(6):730-735 1976

The nature of the humoral reactions of host C3H/He mice against MM2 ascites mammary carcinoma cell-surface components was studied. The components induced three groups of agglutination factors in the host serum, and bound the factors in vitro. The groups were MM2-specific substances, mammary tumor virus (MTV)-associated substances, and tumor-associated embryonic materials. All contained saccharide moieties, and their terminal sugar residues were essential for the binding of the serum factors. These terminal saccharides were exposed during cell proliferation, but masked to some extent in stationary cells, due to elongation of the saccharide moieties. The terminal structures of these polysaccharide moieties of growing and stationary cells were studied by semiquantitative tumor cell agglutination using the agglutinating activities against MM2 cells of MM2-regressor serum and of FM3A/R- and Ehrlich-regressor sera that had partial cross-agglutination activities. Agglutination by phytohemagglutinins, inhibition of the agglutination by saccharides or with isolated cell-surface components, and treatment of the cells with glycosidases were also used for this purpose. (22 refs)

256. INHIBITION OF MAMMARY TUMORS BY INCOMPLETE T-CELL DEPLETION.

Roubinian JR, Blair PB
Dept of Bacteriology and Immunology and the Cancer Res Lab, Univ of California, Berkeley, Ca. 94720
J Natl Cancer Inst; 58(3):727-734 1977

The effects of neonatal and perinatal thymectomy on mammary tumorigenesis in (C57BL x I)F1fC3H hybrid female mice were determined. When hybrid females were neonatally thymectomized by controlled suction, a procedure that removes thymic lobes completely, a large proportion of animals developed stigmas of a fulminant wasting disease and died before tumors developed. However, when hybrid females were subjected to neonatal thymectomy by continuous suction, a procedure that resulted in retention of thymic remnants, they survived and manifested a significant prolongation of latent period before tumorigenesis. When complete removal of the thymus was carried out in the perinatal period, the effect on mammary tumorigenesis was critically dependent on the age at surgery. The procedure was without effect when performed at 1, 3, and 8 weeks of age. However, when it was performed at 9-12 days of age, there was a delay or a decrease in the appearance of mammary tumors. The extent of T-cell depletion and/or its timing in relationship to the introduction of murine mammary tumor virus appeared to play a critical role in determining the effect on eventual tumor development. (26 Refs) (Author Abstract)

257. STIMULATION OF IMMUNE MECHANISMS AGAINST MAMMARY TUMORS BY INCOMPLETE T CELL DEPLETION.

Roubinian JR, Lane MA, Slomich M, Blair PB
Clinical Immunology, Rheumatology Section, Veterans Admin. Hosp., San Francisco, CA 94121
J Immunol; 117(5):1767-1773 1976

The stimulation of immune mechanisms against mammary tumors by incomplete T cell depletion is described. There was no effect on mammary tumorigenesis when BALB/cfC3H female mice were thymectomized by controlled suction; however, the latent period prior to tumor development was increased when the mice underwent continuous suction thymectomy. A complete neonatal thymectomy prevented the immune response to the mammary tumor target cells. The incomplete T cell depletion caused a change in the serum-blocking activity to the tumor target cells, an enhancement of T cell cytotoxicity, and an early onset of non-T cell cytotoxicity. It is concluded that the mammary tumor virus-induced target cell surface antigens may be thymus dependent. (24 refs)

258. EFFECT OF SPECIFIC SOLUBLE TUMOR ANTIGENS ON IMMUNE RESPONSES TO MAMMARY TUMORS IN MICE (MEETING ABSTRACT).

Stutman O
Memorial Sloan-Kettering Cancer Center, New York, NY 10021
Proc Am Assoc Cancer Res; 17():61 1976

Soluble extracts containing mainly viral envelope glycoproteins were obtained by 3M KCl from C3H mammary tumors (MT). Such MT antigens (AG) could produce specific mitogenic responses on immune lymphocytes (L) and could immunize normal C3Hf mice to produce L capable of specific cytotoxicity in vitro against MT or mitogenic responses to MT antigen. When such immune mice were challenged in vivo with MT, differences were observed depending on AG state: crude preparations produced resistance to challenge with MT while a purified fraction rich in viral envelope glycoprotein (GP52) or gp52 from the mammary tumor virus enhanced MT growth. Insolubilized gp52, Con A-gp52 or intact formalinized mammary tumor virus behaved like the crude AG. Both crude or purified, soluble or insoluble AG could interfere with in vitro cytotoxicity when admixed with effector and target cells. When immune L were pre-incubated with soluble crude or purified AG, washed and then added to target, two effects were observed: low AG concentration or short pulses, increased cytotoxicity; high AG concentration or longer (24 hrs or more) incubation times, abolished cytotoxicity. Among the many variables in the system, the physical form of the AG seems critical for elicitation and modulation of immune response in vivo and in vitro. (Author Abstract)

259. CORRELATION BETWEEN THE CLINICAL STATUS OF MICE BEARING MTV INDUCED MAMMARY TUMORS AND THEIR LYMPHOCYTE RESPONSE TO ANTIGEN AND MITOGEN.

Laing CA

Mount Sinai School of Medicine, New York, New York 10029

Proc Am Assoc Cancer Res; 17:183 1976

Immunocompetence of BALB/c (MTV-) mice bearing transplants of MTV induced tumors from BALB/cfC3H (MTV+) mice was measured by the in vitro uptake of ^{3}H thymidine by their splenic lymphocytes in response to PHA and a perchloric acid extract(EMT) of mammary tumors. Tumor bearer lymphocytes showed a depressed response to PHA, stimulation index (SI, (CPM in stimulated cultures/CPM in serum controls) 157 compared to normals SI 696 in the presence of xenogenic sera. The reverse effect was seen when lymphocytes were cultured in syngeneic sera. SI in tumor bearer lymphocytes 171, SI in normal lymphocytes 1.7. Lymphocytes from tumor bearer and normal mice were stimulated by EMT in the presence of xenogeneic sera SI 5.6 and 32.8 respectively or syngeneic sera SI 177 and 2.0 respectively. Excision of the tumor abolished the response of lymphocytes to EMT and restored the response to PHA. Treatment of lymphocytes with anti theta sera or anti immunoglobulin sera plus complement indicate that the PHA response is predominantly T cell mediated while the EMT response is probably B cell mediated. An inverse relationship between the response of lymphocytes from mice in a particular clinical state to PHA and EMT is apparent from these results. (Author Abstract)

260. LYMPHOCYTE RESPONSE TO MAMMARY TUMOR ANTIGENS OF MAMMARY TUMOR VIRUS IN RELATION TO CLINICAL STATUS.

Lopez DM, Sigel MM, Meyers P

Lab. Virol., Dept. Microbiol., Univ. Miami Sch. Med., Miami, Fl

J Natl Cancer Inst; 52(1):289-293 1974

The lymphocyte blastogenic assay based on increased uptake of ^{3}H-thymidine was used to demonstrate lymphocyte responses to antigens derived from a syngeneic transplantable, immunogenic tumor (D1-DMBA-3) initiated by dimethylbenzaanthracene (DMBA) in mice free of mammary tumor virus. The extent of the response was related to the clinical condition of the animals. Responses were evoked in splenic lymphocytes from mice with small tumors but not in cells from mice bearing large tumors. Similarly, the nonspecific response to phytohemagglutinin, also abolished in mice with large tumors, suggested the presence of an immunologic anergy. The cellular responses reappeared after surgical tumor removal or sham surgery. Preparations of nonimmunogenic syngeneic tumors (D1-DMBA-2) also induced by DMBA did not stimulate lymphocytes from tumor-bearing animals or from those whose tumors had been excised. (18 refs)

261. ROLE OF H-2 HISTOCOMPATIBILITY ON GENERATION OF CELL-MEDIATED CYTOTOXICITY AGAINST VIRUS-INDUCED MAMMARY TUMORS IN C3H MICE.

Stutman O

Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY

Transplant Proc; 9(1):1153-1155 1977

The effect of immunization of C3H and C3Hf mice with syngeneic and allogeneic mammary tumors (MT), induced by murine mammary tumor virus (MTV) on their ability to generate a cytotoxic response to syngeneic or allogeneic target cells was evaluated. The response of C3H (MTV+) and C3Hf (MTV-) animals immunized with syngeneic C3H tumors was determined. The MTV+ C3H mice had a vigorous response. When the C3H animals were immunized with allogeneic MT from a DBA/2, A, or RIII (I X C57BL/6)F1 origin, a vigorous response was generated against the syngeneic C3H target cells. The C3Hf (MTV-) animals showed no major differences when immunized with syngeneic or allogeneic MT. When immunized C3H or C3Hf (H-2 kk) mice were tested against allogeneic MT of a DBA/2 (H-2 dd) or RIII (H-2 rr) origin, the percentage cytotoxicity was generally lower than when tested in the syngeneic targets. The results suggest that the increased cytotoxic response observed in C3H (MTV+) mice after immunization with allogeneic MTV+ MT depends on recognition of both the MT virus and the H-2 antigens. (7 Refs)

262. ANTISERUM-COMPLEMENT TREATMENT OF TUMOR-CONTAMINATED SYNGENEIC MOUSE BONE MARROW TRANSPLANTS (MEETING ABSTRACT).

Economou JS, Shin HS, Kaizer H, Santos GW

Johns Hopkins Univ Sch of Medicine, Baltimore, MD. 21205.

Proc Am Assoc Cancer Res; 18:33 1977

The use of autologous bone marrow grafts might permit a wider and more effective application of bone marrow transplantation to clinical cancer therapy. The prior inactivation of possible contaminating tumor cells in the autologous marrow graft may be needed to facilitate therapy. Lethally irradiated (850 - 950 R, whole body) C3H/HeN MTV - mice received an intravenous inoculum of 5 x 10^6 C3H bone marrow cells + 10^4 6C3HED lymphoma cells (of C3H origin). All mice died of tumor by day 13. Prior treatment of this inoculum with a rabbit antiserum raised against 6C3HED (both highly and moderately specific antisera, as tested by complement-dependent cytotoxicity, were used successfully) caused profound tumor suppression (greater than 99.9%) with 50-60% long-term (greater than 60 days) survivors. If the inoculum was pretreated with antiserum and complement, 100% of mice (three experiments) survived greater than 60 days. Sufficient numbers of bone marrow hematopoietic stem cells survived these treatments to repopulate the irradiated hosts. These studies suggest that anti-tumor antiserum and complement might be used to insure that clinical autologous bone marrow grafts are tumor-free. (Author Abstract)

263. IMMUNOLOGY OF SPONTANEOUS MAMMARY CARCINOMAS IN MICE: IMMUNOGENICITY OF MAMMARY TUMOR VIRUS-CONTAINING TISSUES IN MAMMARY TUMOR VIRUS-FREE C3H/2 HOSTS.

Lavrin DH

U. Illinois Med. Ctr., Chicago

Cancer Res; 30(4):1156-1162 1970

The immunogenicity of isogeneic mammary tissue of mammary tumor virus (MTV)-containing C3H/2 mice, hyperplastic alveolar nodules and mammary tumors in MTV-free C3H/2 mice was studied. Specimens of C3H normal mammary tissue and two C3H hyperplastic alveolar nodules grew poorly, or not at all, in adult C3H/2 hosts and gave good protection against further C3H tumor challenge. These tissues did not give protection to immature C3H/2 hosts, and a significant reduction in response was seen in aged hosts. A similar strong reactivity to an MTV-infected C3H/2 mammary tumor by MTV-free mice was seen, but not by mice infected with the virus. It is concluded that MTV is important

in the immunogenicity of normal, pre-neoplastic and neoplastic mammary tissues.

264. INCREASE AND MODIFICATION OF THE CARCINOGENIC POWER OF MAMMARY TUMOR VIRUS AFTER ETHYLENE OXIDE TREATMENT: DISTRIBUTION OF VIRAL PARTICLES.

Thomas JA, Lambre C, Henry M
Lab. Biol., U. Paris, France
C R Acad Sci D (Paris); 273(18):1650-1653 1971

An attempt was made to immunize mice against the mammary tumor virus (MTV) following its presumed attenuation by ethylene oxide. Mammary adenocarcinoma inoculum (T III strain) treated with 0.5% ethylene oxide and 10% glycerol was administered ip to young male and female mice (Swiss, CD1 and LAB) in three injections of 0.5 ml each (second and third injections after 13 and 29 days, resp). Control animals received the same inoculum without ethylene oxide. In 37.5% of the 80 Swiss mice, tumors were observed between the 14th and 550th days; the corresponding percentage for the control group was 11.8%. Mammary adenocarcinomas were observed in 22 cases, with typical metastases in nine cases. Pulmonary metastases were relatively large, and cancer dissemination was very frequent in the thorax and abdomen. Regression of the primary mammary cancer with small residual adenocarcinoma was observed in one case. Adenocarcinomatous metastases without anatomically ascertained mammary adenocarcinoma were found in five cases. Virologic investigations of primary mammary carcinomas with and without metastasis revealed the presence of both A and B forms of MTV particles; the B form was predominant in histologically typical metastases, particularly in the lung. Forms A and B were detected in adenocarcinomatous metastases with atypical mammary structure. MTV particles were found in anaplastic liver and spleen carcinomas and in mesenteric metastases. Leukemic C particles were found in the thymus of a mouse bearing anaplastic carcinoma of the liver and spleen. Other particles, not yet identified, also occurred in a spleen carcinoma. Both A and B forms MTV were present in the control group. Treatment of the MTV with ethylene oxide seems to have enhanced rather than diminished its carcinogenicity.

E. Alteration of Immunocompetence by MuMTV

265. ALTERATION OF IMMUNOCOMPETENCE BY MAMMARY TUMOR VIRUS.

Griswold DE, Heppner GH, Calabresi P
Roger Williams Gen. Hosp., Providence, R.I.
J Natl Cancer Inst; 50(4):1035-1038 1973

Methylated bovine serum albumin (MBSA)-induced hypersensitivity and antisheep red blood cells (SRBC) hemolysin responses were studied in C3H/HeJ mice harboring mammary tumor virus (MTV) and an MTV-negative companion strain, C3HfB/HeJ. Only [illegible]B/HeJ mice produced appreciable hypersensitivity to [illegible]A, as measured by paw edema. Production of 7S h[illegible]n plaque-forming cells (hpfc) to SRBC was comparab[illegible]e two lines, but C3HfB/HeJ mice produced higher n[illegible]rs of 19S hpfc to SRBC. Foster-feeding of C3HfB/HeJ mice on MTV-infected C3H/HeJ mothers resulted in animals with diminished capacity to produce an MBSA-induced hypersensitivity but without impairment of SRBC-induced hemolysin production. Virus infection increased the ability of female mice to produce 7S hemolysin. Thus the effect of MTV on immunocompetence is more complex than a simple immunosuppression.

266. IMMUNOLOGIC DEFICIENCY ASSOCIATED WITH MAMMARY TUMOR VIRUS (MTV) INFECTION IN MICE: HEMAGGLUTININ RESPONSE AND ALLOGRAFT SURVIVAL.

Blair PB, Kripke ML, Lappe MA, Bonhag RS, Young L
Sept. Pact., Immun., U. California, Berkeley
J Immunol; 106(2):364-370 1971

Female mice infected with mammary tumor virus (MTV) prior to immunization with sheep red blood cells showed lower mean hemagglutinin antibody titers than did immunized mice not infected with MTV. Immunized mice which were not infected produced high hemagglutinin titers (peaks at 9000-13000) 30 days after immunization with sheep erythrocytes. Six-month-old mice produced higher hemagglutinin titers than 8, 10 or 12-month-old-mice. BALB/c mice developed higher mean titers than did BALB/cfC3H mice. Mice injected with MTV 4 days prior to immunization developed lower hemagglutinin titers than did uninfected mice; in both groups maximum titers were attained 5-7 days after immunization. Uninfected mice had mean hemagglutinin titers of 8.14 (log2 titer), while infected mice had mean titers of 5.29. Differences between infected- and uninfected-hemagglutinin titers were statistically significant only for serum samples collected from 7-month-old mice. Skin allografts survived longer on virus-infected mice than on uninfected mice. Immunologic deficiency was generally more pronounced in infected mice 10 months of age and older than in younger animals.

267. ENHANCEMENT OF BLOCKING FACTOR PRODUCTION BY MAMMARY TUMOR VIRUS (MTV) INFECTION (MEETING ABSTRACT).

Griswold D, Heppner G, Calabresi P
Roger Williams Gen. Hosp., Providence, R.I.
Proc Am Assoc Cancer Res; 15:112 1974

The ability of MTV to diminish effective cell-mediated immunity (CMI) may be an important factor in its carcinogenic activity. MTV C3H mice develop weaker delayed hypersensitivity to methylated bovine serum albumin (MBSA) than do MTV- mice of the same genotype. Since MBSA-induced hypersensitivity has a humoral blocking factor production or decreased CMI. Cytosine arabinoside (ara-C) treatment of C3H/HeJ (MTV mice in a regimen designed to inhibit only humoral immunity and leave CMI intact, enabled these mice to respond with the same strength as C3HeB/FeJ (MTV-) mice. C3H/HeJ mice demonstrated a 106% increase of MBSA-induced edema with ara-C treatment. The response was not different from that seen in C3HeB/FeJ, ara-C treated mice. These data suggest that in C3H/HeJ mice, MTV compromises hypersensitivity largely by enhancing blocking factor production. Removal of blocking factor by ara-C reveals a relatively normal CMI response. This activity of MTV would create an ideal immunological environment for neoplastic transformation and growth.

268. STUDIES ON INTERFERON INDUCTION BY THE MOUSE MAMMARY TUMOR VIRUS (MEETING ABSTRACT).

Came PE, Moore DH
Schering Corp., Bloomfield, N. J.
Proc Soc Exp Biol Med; 133(1):252-254 1970

Serum from female C57BL/Haag and male Swiss mice, inj iv with 0.1 ml mouse mammary tumor virus (MTV; about 1010-1012 particles), milk from lactating mice (containing as much as 1012 MTV particles/ml), and concentration meedium from the CCL-51/MMT 060562 cell line (actively producing MTV) were assayed for interferon by the plaque inhibition test, with negative results. MTV failed to induce resistance in male Swiss mice to challenge with Columbia SK virus, and no

specific hemagglutinin activity (HA) could be found. It is concluded that although MTV shares other properties with the myxoviruses, it lacks HA activity and interferon-inducing capacity.

269. CORRECTION OF A MURINE MAMMARY TUMOR VIRUS-ASSOCIATED IMMUNOLOGICAL DEPRESSION BY SELECTIVE IMMUNOSUPPRESSION WITH CYTOSINE ARABINOSIDE.

Griswold DE, Kopp JS, Manning JS, Heppner GH
Dept. Med., Roger Williams Gen. Hosp., Providence, R.I.
Cancer Res; 35(10):2670-2673 1975

The relative roles of cell-mediated immunity (CMI) and humoral immunity in the diminished hypersensitive reaction to methylated bovine serum albumin, associated with mammary tumor virus infection in mice, is reported. Since oxazolone-induced contact sensitivity and phytohemagglutinin-induced lymphocyte stimulation were both normal, or slightly increased, in mice infected with mammary tumor infection, it is concluded that CMI is not involved. However, treatment of mice with cytosine arabinoside on a regimen that affects only humoral immunity and leaves CMI intact (20 mg/kg/d on d. 1-5 of the 14 d sensitization period for methylated bovine serum albumin hypersensitization) corrected the immunological deficit in infected mice. It is suggested that infection with mammary tumor virus may result in increased production of blocking humoral immunity. (16 refs)

F. Tumor Antigens Associated with MuMTV

270. EXPRESSION OF MAMMARY TUMOR VIRUS ANTIGEN ON THE MEMBRANES OF LYMPHOID CELLS.

Gillette RW, Robertson S, Brown R, Blackman KE
Meloy Labs., Springfield, Va.
J Natl Cancer Inst; 53(2):499-505 1974

An indirect immunofluorescent technique and a 51Cr release toxicity assay were used to detect mouse mammary tumor virus (MMTV) antigens on BALB/c, C57BL/6, RIII, C3H/He, DD/He, AKR, and NIH Swiss mouse lymphoid cells. MMTV expression was greatest in lymphoid cells of splenic, lymph node, and peritoneal origin. The quantitative levels of surface antigen expression in these cells correlated strongly with the levels of virus excretion in milk and mammary tumor formation in high-virus expressor strains such as C3H/HeN, RIII, and DD/He. The percentage of MMTV-positive lymphoid cells increased with the age of the animal; it rose markedly shortly after birth in all strains, but reached higher levels earlier in the strains with the greatest natural mammary tumor incidence. All strains examined expressed MMTV cell-surface antigen, but the low-expressor strains expressed it at markedly lower levels. The relative absence of MMTV in the thymus, the pattern of distribution in other lymphoid organs, and the sensitivity of positive cells to anti-IgM and anti-MMTV but not anti-theta serum suggested that MMTV structural components were expressed on the lymphoid cells and that this was associated primarily with the bone marrow-derived lymphocytes.

271. MAMMARY TUMOR VIRUS ASSOCIATED ANTIGENS ON THE MEMBRANE OF INFECTED MOUSE SPLEEN CELLS.

Daams JH, Calafat J, Lasfargues EY, Kramarsky B, Bentvelzen P
Netherlands Cancer Inst., Amsterdam
Virology; 41(1):184-186 1970

Tissue cultures were initiated from the spleens of 6-week-old C57BL and BALB/c mice infected with mammary tumor virus (MTV) by foster nursing on RIII milk. All cell suspensions from cultures at the time of transfer showed the presence of an MTV antigen at the cell membrane and in the cytoplasm. MTV membrane antigen was confirmed in BALB/cfRIII spleen cells after 16 weeks and in C57BLfRIII spleen cultures after 20 weeks. It is concluded that the MTV genome must be maintained in spleen cells. The MTV genome is unable to cause production of complete viral particles but seems to control antigen production at the cell surface.

272. EXPRESSION OF NORMAL MAMMARY EPITHELIAL CELL ANTIGENS IN MAMMARY NEOPLASIA (MEETING ABSTRACT).

Ceriani RL, Peterson JA, Abraham S
Bruce Lyon Mem. Res. Lab., Children's Hosp. Med. Ctr., Oakland, CA 94609
Proc Am Assoc Cancer Res; 18:160 1977

Antibodies that recognize differentiation antigens of mouse mammary epithelial cells (MMEC) were raised in rabbits and can be used to detect the expression of normal mammary antigens in mouse mammary tumor cells. These antisera were prepared against membranes of BALB/c mouse milk fat globules (MMFG). After absorption with mouse blood cells, liver, and fetal fibroblasts these antisera specifically detect, by indirect immunofluorescence, normal mid-pregnant and lactating MMEC, MMFG and all mouse epithelial mammary tumor cells tested (either MuMTV + or -), albeit with different intensities. Mammary tumor cells from BALB/c, C3H, RIII, or GRS/A mice all give a positive response. These antisera are not tumor specific, since they do not bind to other types of tumor cells (colon, lung, and ovarian carcinomas, and melanomas), but appear to be tissue specific since they do not bind to BALB/c mouse salivary gland, fibroblasts, liver, kidney, spleen, brain or blood white cells. Thus, the expression of MMEC cell surface differentiation antigens in transformation and tumor progression can be detected with these antisera. They are also useful in cell type identification in tissue culture and in biochemical and genetic studies of mammary cell surface components. (Author Abstract)

273. EXPRESSION OF THY 1 ANTIGEN IN NORMAL AND NEOPLASTIC MAMMARY CELLS OF MICE.

Gillette RW
Cancer Center of Hawaii, Univ of Hawaii at Manoa, 1997 East-West Rd, Honolulu, HI 96822
J Natl Cancer Inst; 58(6):1629-1633 1977

The expression of Thy 1.2 (thetaC3H) antigen was measured on the membranes of normal and neoplastic RIII and C3H mammary cells. Competitive inhibition assays revealed that the average membrane content of Thy 1.2 in mammary tissues was about equal to that of lymph node cells. Higher percentages of Thy 1.2-positive cells than mammary tumor virus (MuMTV)-positive cells were observed by immunofluorescence, which suggested that not all the Thy 1.2-positive cells recovered from tumors were also MuMTV-positive. Established tissue culture cell lines C3H and RIII MT expressed lower levels of Thy 1.2 than did cells from mammary tumors. Treatment with the synthetic glucocorticoid dexamethasone increased the average Thy 1.2 expression in cultured mammary tumor cells as well as the levels of RNA-directed DNA polymerase. Since the percentages of Thy 1.2-positive cells also were greater in steroid-treated cultures, while fewer cells were needed to absorb a standard amount of anti-Thy 1.2 activity, it was concluded that dexamethasone enhanced membrane Thy 1.2 expression as well as MuMTV production by the cultured cells. (18 Refs) (Author Abstract)

274. LEVELS OF MAMMARY TUMOR VIRUS IN HORMONE-DEPENDENT AND -INDEPENDENT MOUSE MAMMARY TUMOR CELLS.

Sluyser M, Nouwen T, Hilgers J, Calafat J
Div. Endocrinology, Netherlands Cancer Inst., Antoni van Leeuwenhoek-Huis, Amsterdam, Netherlands
Cancer Res; 37(7):1986-1990 1977

Levels of mammary tumor virus particles (types A and B) and levels of the virus antigen were assayed in hormone-dependent and -independent mammary tumors of GR mice. Various transplant generations of seven separate tumor lines were investigated. The results indicated that the tumors consisted of different cell clones, each of which exhibited a separate progressive expression and subsequent loss of the mammary tumor virus. When the tumors were transplanted, levels of B particles first declined in the hormone-dependent cells, but in later transplant generations, the B particle content of the autonomous cells also dropped. In some tumor lines, this was accompanied by a decrease in viral antigen and/or A particles, but in other lines these concentrations remained high. One tumor line (line V) that remained hormone-dependent throughout nine transplantations was practically devoid of B particles but contained high levels of A particles and mammary tumor antigen. (Author abstract) (13 Refs)

275. DISTRIBUTION AND ANTIBODY-INDUCED REDISTRIBUTION OF A MAMMARY TUMOR VIRUS-INDUCED AND A NORMAL ANTIGEN ON THE SURFACE OF MOUSE LEUKEMIA CELLS.

Hilgers J, van Blitterswijk WJ, Bont WS, Theuns GJ, Nusse R, Haverman J, Emmelot P
Netherlands Cancer Inst., 108 Sarphatistraat, Amsterdam-1004, Netherlands
J Natl Cancer Inst; 54(6):1335-1342 1975

With the indirect membrane immunofluorescence test, the distribution and antibody-induced redistribution (patching and capping) of a mammary tumor-virus-induced (MLr) and a normal (Thy 1.2) cell-surface antigen were compared on GR mouse thymocytes and leukemia (GRSL2). AKR mice were immunized with thymocytes from C3Hf mice to produce antiserum against Thy 1.2. At O C Thy 1.2 fluorescence was ringlike and more intense on GRSL2 cells than on thymocytes, whereas MLr fluorescence on GRLS2 cells was patch-like and brighter than Thy 1.2 fluorescence. At 20 or 37 C, capping of Thy 1.2 on both cell types was readily achieved but MLr capping occurred only in a few GRSL2 cells and was less pronounced. However, after addition of the secondary antibodies, MLr capping was markedly increased by gradual cooling of cells to about 17 C. Conversely, after addition of antibodies at O C, gradual warming of cells under the fluorescence microscope resulted in extensive capping both of MLr and Thy 1.2 at 13-14 C. Rapid cooling or rapid warming led to almost instantaneous capping. These results may be explained by the occurrence of phase transitions or phase separations in the lipid domain of the plasma membranes, within the particular temperature range. Thy 1.2 caps were small and eventually were endocytosed, whereas the MLr caps were large and were exfoliated from the cells.

276. DISTRIBUTION OF VIRUS PARTICLES AND MAMMARY TUMOR VIRUS ANTIGENS IN MOUSE MAMMARY TUMORS, TRANSFORMED BALB/C MOUSE KIDNEY CELLS, AND GR ASCITES LEUKEMIA CELLS.

Calafat J, Buijs F, Hageman PC, Links J, Hilgers J, Hekman A
Netherlands Cancer Inst., Amsterdam
J Natl Cancer Inst; 53(4):977-991 1974

The distribution of virus particles and mammary tumor virus antigens was investigated in mammary tumor cells from BALB/c mice infected with mammary tumor virus (MTV), baby BALB/c mouse kidney cells (BMK) transformed with 3-methylcholanthrene (A3 cell line) or MTV (A5 cell line), and GR mouse ascites leukemia cells (GRSL). B and C particles, as well as budding particles, were observed in A3 and A5 cells; the number of B particles decreased and the number of C particles increased after several passages. During early transplant generations of GRSL cells, only intracytoplasmic A particles and some budding particles were seen; after one yr of transplantation, mature B and C particles were observed. Immunoferritin labeling with rabbit anti-MTV serum showed that the distribution of MTV antigens was similar in the four types of cells; budding, immature, and mature B particles were labeled. In addition, labeled MTV antigens were found in small distinct areas over the whole surface of unpolarized cells. When cells were polarized, as shown by increased membrane activity (formation of pseudopodia and microvilli) at one pole, the label was more abundant and density packed at this pole. The presence of B and C particles in the chemically transformed BMK cells confirms the existence of an endogenous MTV and murine leukemia virus in BALB/c mice.

277. IMMUNOLOGICAL CROSS REACTIONS BETWEEN VIRUS PRODUCING AND NONVIRUS PRODUCING MAMMARY CARCINOMAS IN MICE.

Zotter ST, Kemmer C, Muller M, Micheel B
Med. Acad. Carl Gustav Carus, Dresden, East Germany
Arch Geschwulstforsch; 40(1):23-34 1972

Immunological cross reactions are described between mammary tumor virus (MTV)-producing mammary tumors (MT) and an apparently virus-free MT, which indicate the existence of a virus-coded cell antigen in these tumors. The studies were carried out with four MTs from syngeneic CBA/Bln mice immunized with a purified MTV preparation. Two carcinomas (MT 4814/24 and MT 8020/15) were virus-free, virus production could not be definitely demonstrated in a third carcinoma (MT 9915/5), and one which had been transformed since the sixth generation and originated from a virus-containing tumor (MT 7782/11) had become virus-free. The membrane immune fluorescence test was positive for tumors MT 4814 and 8020 and negative for MT 9915 and 7782. During the examination of the cell suspensions under the electron microscope, budding and mature MTV particles were seen in MT 4814 and 8020, following incubation with syngenic hyperimmune sera. In addition to virus labeling, deposits of ferritin complexes were seen in the virus-containing tumors; MT 9915 cell membrane was similarly marked. Normal CBA serum showed no membrane deposits of this nature, the ferritin complexes occurring in random fashion with no relationship to the cell membrane. Ferritin labeling was not seen in the transformed MT 7782. Growth of MT 8020 and MT 9915 was significantly inhibited by mixtures with hyperimmunized spleen and peritoneal cells from CBA female mice, whereas growth of MT 7782 was not affected by these cells.

278. SEARCH FOR CROSS-REACTING ANTIGENICITY BETWEEN MAMMARY TUMOR VIRUS-INDUCED MAMMARY TUMORS AND EMBRYONIC ANTIGENS: EFFECT OF IMMUNIZATION ON DEVELOPMENT OF SPONTANEOUS MAMMARY TUMORS.

Blair PB
U. California Cancer Res. Genet. Lab., Berkeley
Cancer Res; 30(4):1199-1202 1970

Experiments performed on female BALB/cfC3H mice, infected with mammary tumor virus from allogenic (A/Crgl) or syngenic (BALB/cCrgl and BALBcfC3HCrgl) tissue, offered no evidence for the presence of embryonic antigens in mouse mammary tumors. Pretreatment with embryonic

extracts or tissue implants had little or no effect on tumor development in experimental animals. Mice were immunized with antigen from a spontaneous mammary tumor; with a mammary gland extract from a lactating female; and with tissue extracts and implants from embryos, newborns and adult mammary glands.

279. MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGENICITY OF L-1210 MURINE LEUKEMIA CELLS.

Kisielow P, Radzikowski C, Steuden J, Szkudlarek J, Krawczynski K
Inst. Immun. Exp. Therapy, Polish Acad. Sci., Wroclaw
Arch Immunol Ther Exp (Warsz); 19:789-799 1971

Sera of BALB/c mice (which carry the same H-2 antigens as DBA/2 mice) injected with leukemia L-1210 cells showed cytotoxic activity against these cells. The antiserum was not cytotoxic to normal peritoneal cells of DBA/2 mice. The cytotoxic activity of BALB/c anti-L-1210 serum could be removed only by means of mammary tumor cells from DBA/2 or C3H mice known to be naturally infected with mammary tumor virus (MTV). This and the finding that L-1210 cells were insensitive to the cytotoxic action of antisera for other virus-associated antigens of murine leukemias suggested that L-1210 cells carry mammary leukemia antigen. Anti-L-1210 sera were also obtained from MTV-negative as well as MTV-positive DBA/2, BALB/c and (DBA/2xBALB/c) mice. These results indicate that neonatally infected mice could produce humoral antibodies against MTV-associated antigens, in spite of the presumed specific immunological tolerance of such animals.

280. IMMUNOFLUORESCENCE AND IMMUNOELECTRON MICROSCOPY OF VIRUS-INDUCED MAMMARY TUMORS IN MOUSE LINE CBA/BLN.

Zotter S, Muller M, Kemmer C
Carl Gustav Carus Med. Acad., Dresden, Germany
Vopr Onkol; 19(11):22-28 1973

By using the indirect immunofluorescence test with syngeneic, allogeneic and xenogeneic antisera, it has been demonstrated that cross-reacting antigens to murine mammary tumor virus (MTV) are present in many tumors in CBA/Bln mice infected with MTV and in sera of mice immunized with MTV. This antigen is not identical with virions or virus particles of mouse MTV. Although the antigen content remained relatively constant over a long period in some tumors, in one tumor antigen only began to appear with the sixth mouse passage, and no evidence of virus particles has yet been detected with the electron microscope. Tumors containing no virus particles apparently do contain the viral genome and virus-coding surface antigens. Another tumor which used to produce virus and underwent sarcomatous degeneration still has no evidence of antigen.

281. STUDIES ON THE IMMUNOGENICITY OF PRENEOPLASTIC AND NEOPLASTIC MAMMARY TISSUES OF BALB/C MICE FREE OF THE MAMMARY TUMOR VIRUS.

Weiss DW, Sulitzeanu A, Young L, Adelberg M, Segev Y
Dept. Immun., Hebrew U.-Hadassah Med. Sch., Jerusalem, Israel
Isr J Med Sci; 7(1):187-201 1971

Highly inbred BALB/cCrgl mice, free of mammary tumor virus were given sc immunizing implants of 1 mm3 fragments of living tumor or living normal lactating mammary tissue derived from an isogenic nursing female or normal tail skin grafts taken from the tumor donors, which were surgically removed when tumors reached an approximate size of 5 x 5 mm or after a period of 4 wk. Ten days later, sera were pooled by groups; the animals were challenged by sc injection into the left inguinal region of a freshly prepared suspension of viable tumor cells. A pronounced increase in the incidence of progressive tumors as a function of time resulted after challenge in the tumor-immunized group. Repeat experiments using tumor tissue in the 9th transplant generation compared to the 4th of the initial experiment, revealed no significant differences in tumor incidence between the differently pretreated groups; 50 to 75% of the mice developed cancers and the growth rate in the tumor-and lactating mammary gland-immunized groups was moderately enhanced. Animals receiving pooled sera 6 hr before challenge with tumor cells developed tumors somewhat later with a slightly lowered incidence in the mice given serum from the tumor bearers. Challenge of animals with 5 other types of tumor cells and heart-kidney fragments (used as controls) revealed generally no difference in the incidence of tumor development; however, a time-related enhancement or repression of tumor growth following challenge was seen after immunization with pooled sera.

VI. MAMMARY TUMORIGENESIS

A. Occurrence and Growth of Spontaneous Mammary Tumors

282. UNUSUALLY HIGH INCIDENCE OF SPONTANEOUS MAMMARY CARCINOMATA IN A COLONY OF BALB/C MICE.

Fieldsteel AH, Dawson PJ, Kurahara C, Brooks RE
Stanford Res. Inst., Menlo Park, CA 94025
Br J Cancer; 32(6):741-744 1975

An unusually high incidence of spontaneous mammary tumors in a colony originating from the BALB/cCrgl mouse subline is reported. During a 6 yr observation period (1967-1972), 51.5% of 582 breeding females developed mammary tumors at a mean age of 10.7 +- 2.8 mo. The incidence peaked at 75.7% in 1968 and declined to 27.8% in 1971, but rose again to 51.2% in 1972. All but one of 38 tumors belonged to Dunn's type B adenocarcinoma. The largest group (18 tumors) was predominantly glandular with small cysts and solid areas. All of six tumors examined ultrastructurally contained large numbers of type B virus particles. The data suggest that mammary tumor virus was transmitted vertically.

283. ACTINOMYCIN D AND X-RADIATION SUPPRESSION OF SPONTANEOUS TUMORIGENESIS IN MICE.

Mason JM, Jennings BR
Univ. Tenn. Med. Units, Dept. Pathol., Memphis, Tenn.
J Reticuloendothel Soc; 15(2):96-111 1974

The effect of actinomycin D (AD; 4 microg) and/or 100 R x-radiation on the development of spontaneous mammary tumors in Swiss mice of the Hale-Stoner strain was evaluated. Active immunization against sheep RBC was by intra-abdominal injection (0.1 ml) 10% sheep RBC in 0.15 M NaCl. Mammary tumors were excised, fixed with formalin and stained for routine histologic analysis. Admin of AD alone, x-radiation alone, or a combination of the two treatments at 6 to 8 wk of age had no significant effect on the percentage of animals developing mammary tumors over a 10 mo period relative to non-treatment controls. Five weekly admin of AD and x-radiation beginning at 6 wk of age caused a 99% suppression of sheep hemagglutinins for 3.9 d relative to untreated control mice. Treatment with AD and x-radiation (5x) significantly decreased the incidence of mammary tumors and delayed their appearance for 6 mo. Those mice with a serum hemagglutinin titer (SHT) of 1:4,096 or higher had significantly higher incidence of mammary tumors after 300 d of age than those with a SHT of less than 1:2,048. Similar

results with SHT were obtained when those mice receiving immunosuppressive treatment were excluded from the analysis. AD and x-radiation given at 4 weekly doses to 170 d old mice had no effect on tumor incidence. Weekly treatments (4x) of AD and x-radiation beginning at 3.8 mo of age had no effect on tumor incidence; treated mice tended to develop tumors prior to untreated control. AD and x-radiation (5x), 8 d and 1 d before and 6 d, 13 d and 20 d after tumor isografts had no effect on the incidence of tumor takes relative to untreated control mice; treated animals achieved the control incidence at a later time (50 d). Weekly admin of AD and x-radiation (5x) slightly altered the growth rate of mammary tumors; treatment failed to alter the appearance of new tumors, indicating that treatment resulted in no tumor cell toxicity. Treatment (4x) had no discernible histologic effects on the tumors except that lymphoid elements were confined solely to the stroma in untreated tumors. (41 refs)

284. POSITIVE CORRELATION OF CHEMOTHERAPEUTIC RESULTS IN HUMAN AND MURINE SOLID CARCINOMA.

Martin DS, Fugmann RA, Hayworth PE, Davin ER
Cathol. Med. Cent., Woodhaven, N.Y.
Proc Am Assoc Cancer Res; 15:66 1974

285. INFLUENCE OF IMMUNOSUPPRESSION ON THE GROWTH OF TRANSPLANTS OF SPONTANEOUS MAMMARY TUMOURS IN MICE. (NEONATAL OR ADULT THYMECTOMY/CYCLOPHOSPHAMIDE/WHOLE-BODY IRRADIATION/ALS/VIRUS-FREE (C57BL X C3H)F(1) HYBRIDS).

Gruntenko EV
Inst. Cytol. Genet., Sib. Branch Acad. Sci., Novosibirsk, U.S.S.R.
Folia Biol (Praha); 19(6):414-419 1973

A variety of treatments significantly suppressed growth of syngeneic mammary tumors transplanted to C3H/He male and A/HeJ male and female mice infected with mammary tumor virus: thymectomy at age 6 d; cyclophosphamide (1 mg on d 1 before and d 1 after transplant); 300 R total body irradiation prior to transplant (no synergism was observed between thymectomy + cyclophosphamide or thymectomy + irradiation); admin of antilymphocyte globulin subsequent 750 R total body irradiation (d -10) and admin of 2 x 10^6 bone marrow cells on d -9 before transplant. The latter treatment did not suppress growth of a chemically-induced hepatoma in mice. In virus-free hybrids (C57BL x C3H)F(1) thymectomy at age 6 d stimulated the growth of transplanted mammary tumors. It is suggested that the growth of mammary tumor transplants is immunologically enhanced in virus-infected animals. (16 refs)

286. SPONTANEOUS MURINE MAMMARY ADENOCARCINOMA: MODEL SYSTEM FOR EVALUATION OF COMBINED METHODS OF THERAPY.

Stolfi RL, Martin DS, Fugmann RA
Catholic Med. Ctr. Brooklyn Queens Inc., Jamaica, N. Y.
Cancer Chemother Rep; 55,Pt1(3):239-251 1971

Spontaneous mammary adenocarcinomas in female (BALB/cfC3H x DBA/8)F1 hybrid mice (carrying the mammary tumor virus) are not curable by surgery, immunotherapy or chemotherapy alone, but evidence is presented to demonstrate that these modes of treatment potentiate each other. Best results were noted with a combination of immunotherapy (zymosan), surgery and a combination of 4 or 5 antitumor agents (streptonigrin, 6-thioguanine, cyclophosphamide, actinomycin D, mitomycin C), which resulted in lifetime local and absolute cure rates of 65% and 31%, resp.

287. INHIBITION OF SPONTANEOUS MAMMARY CARCINOMA OF MICE BY TREATMENT WITH INTERFERON.

Came PE, Moore DH
Schering Corp., Bloomfield, N. J.
Proc Soc Exp Biol Med; 137(1):304-305 1971

Admin of polyinosinic:polycytidylic acid (poly-I:poly-C; 100 MUg/wk x 35-42) or interferon (1000-2500 IU./wk x 35-42) reduced the incidence of spontaneous mammary carcinomas in RIII mice; poly-I:poly-C also significantly lowered the rate of tumor development. However, milk samples from all mice were positive for the mammary tumor virus (MTV) antigen by the second lactation. Results suggested that the tumors were inhibited by endogenous and exogenous interferon, although no concomitant inhibition of MTV occurred.

288. BIOLOGICAL PROPERTIES OF MOUSE MAMMARY TUMOR VIRUSES (MEETING ABSTRACT).

Moore DH
Institute for Medical Research, Camden, NJ 08103
Proc Am Assoc Cancer Res; 17():40 1976

Milks from various mouse strains were titrated for infectivity in several mouse strains. Some strains carry two mammary tumor viruses, each discernible by its mouse strain preference in infectivity tests. One of the viruses can be removed by foster nursing, but the other cannot. Most Af, C3Hf, and RIIIf breeders of high parity shed infectious MTV in their milks, provided a suitable assay mouse strain is used. 90% of high-parity C3Hf mice shed MTV in their milks, but no clear-cut differences in infectivity between C3H and C3Hf milks tested in several assay strains could be detected. A substrain of C57BL/RIII has been started. The viral antigen (in 3rd parturition milks) incidence and mammary tumor incidence in these C57BL mice has been 80-100% for 6 generations. C57BL mice are also susceptible to GR virus but are relatively resistant to other viruses tested. They are especially resistant to RIIIf virus, to which Af and BALB/c mice are very susceptible. (Author Abstract)

289. MOUSE MAMMARY TUMOR VIRUS INFECTIVITY AS A FUNCTION OF AGE AT INOCULATION, BREEDING, AND TOTAL LAPSED TIME.

Moore DH, Charney J, Pullinger BD
Inst. Med. Res., Camden, N. J.
J Natl Cancer Inst; 45(3):561-565 1970

Mouse mammary tumor virus-containing milk (tumor incidence, 84%) was injected ip into tumor- and virus-free mice from 2-12 wk after birth at doses of 0.2 ml/mouse to investigate the effect of inoculation age on viral infection and its correlation with the eventual development of mammary tumors; antigen was assayed with rabbit anti-mammary tumor virus antiserum on micro-Ouchterlony plates. Over the age range of 2-10 wk, the total lapsed time from inoculation to the appearance of antigen in the milk or the development of tumors was approximately constant, irrespective of age at inoculation; however, inoculation at 12 wk of age gave a relatively lower incidence of infection and tumor development. All age groups had a gradual increase in antigen incidence from the first to the third lactation. Force-breeding to the second or third lactation of mice inoculated at age 10 and 12 wk did not shorten the lapsed time for obtaining equivalent antigen incidences. Inoculation during first pregnancy gave negative antigen-assay results at the third and even at the sixth lactation. Inoculating mice at ages between 4 and 10 wk, mating them at 10-12 wk, and testing their milk at the second lactation gave a practical assay requiring about 15 wk.

290. FATE OF MOUSE MAMMARY TUMOR VIRUS (M-MTV) TRANSMITTED TO NEWBORN X/GF MICE (MEETING ABSTRACT).

Goldfeder A
Delafield Hosp., New York, N.Y.
Proc Am Assoc Cancer Res; 15:78 1974

The experiment was designed to document the oncogenicity of MMTV. The question has been posed: What is the fate of MMTV after transmission by foster nursing? X/Gf mice, producing no mammary tumors spontaneously, were challenged with MMTV by foster nursing on DBA/212 mothers carrying MMTV. Some foster-nursed X/Gf mice developed mammary tumors. Analysis of these tumors on a molecular level provided evidence of the intimate interaction of genetic material of MMTV with that of the host target cell. Extracts of the mammary tumors contained viral specific high molecular wt 70S RNA and reverse transcriptase. The putative virus complex was localized in sucrose gradients at a density of 1.16 g/ml, the position characteristic of RNA tumor viruses. Parallel electron microscopic (EM) studies of these tumors revealed the characteristic type MMTV particles. Both molecular and EM studies provide credible evidence of viral etiology of the X/Gf mammary tumors and document unequivocally the oncogenicity of MMTV.

291. MAMMARY CARCINOGENESIS IN FOSTER-NURSED X/GF MICE.

Goldfeder A, Ghosh AK
Delafield Hosp., New York, NY
Cancer Res; 34(9):2184-2191 1974

Newborn X/GF mice were foster nursed by mothers of the DBA/212 mouse strain. (The X/Gf mice are highly resistant to the spontaneous development of mammary tumors, whereas DBA/212 mice develop mammary tumors at high rates and contain an abundance of the mammary tumor virus (MMTV). Varied numbers of F1 to F7 generations of foster-nursed females produced mammary tumors at ages from 12-24 months. Sections of the tumors stained with hematoxylin and eosin and studied by light microscopy showed the characteristic appearance of mammary carcinomas, although differing in degree of differentiation. Electron microscope studies revealed the characteristic type MMTV particles in the tumors. Morphologically, the virus particles in X/Gf mammary tumors appeared identical to those seen in spontaneous mammary tumors of the DBA/212 foster mothers. Separate biochemical studies on molecular level of growing X/Gf tumor extracts revealed viral-specific high-molecular-weight 70 S RNA and reverse transcriptase; the putative viral complex was localized in sucrose gradients at a density of 1.16 g ml, the position characteristic of RNA MMTV. Thus, the electron microscope and biochemical data on a molecular level provide documentary evidence of the infectivity of the MMTV in the host cells. X/Gf mice, challenged with MMTV by foster nursing, produced mammary tumors in early generations but failed to develop tumors after the seventh generation. This suggests that the X/Gf host, known to generate high levels of antibodies against MMTV, may be responsible for the cessation of mammary tumor development and not the virus. The significance of the immune competence of the host in neoplasia thus becomes apparent.

292. STRAIN C3H-AVYFB MICE: NINETY PERCENT INCIDENCE OF MAMMARY TUMORS TRANSMITTED BY EITHER PARENT.

Vlahakis G, Heston WE, Smith GH
Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, MD
Science; 170(3954):185-187 1970

Foster nursing and hybridization experiments were performed with strain C3H-AvyfB mice, which are highly susceptible to mammary tumors (incidence approaching 90% by 15 months-of-age), to determine whether this susceptibility is transmitted in milk via a mammary tumor virus, or in factors transmitted at conception. Reciprocal matings were effected between the susceptible strain of mice, and a strain having a low incidence of mammary tumors. In addition, low-incidence mice were nursed by high-incidence females, to investigate the possibility of milk transmission of a mammary tumor viral agent. The result of reciprocal hybridization between susceptible C3H-AvyfB mice and less susceptible mice gave no evidence of a maternally transmitted agent implicated as the cause of a high incidence of mammary tumors in the former strain; there was a high tumor incidence in both reciprocal groups (highest incidence in the F1 generation, 96.3%, lowest, 57.9%). There was no evidence of a mammary tumor virus transmitted to unsusceptible mice in the milk of susceptible nursers; tumor incidence in unsusceptible mice so nursed was only 7.7%. It may be that the factor responsible for a high incidence of mammary tumor in C3H-AvyfB mice is the Avy gene, which may increase the virulence or transmissibility of a variety of mammary tumor virus transmitted vertically by either parent.

293. ATTEMPTS TO DETECT NODULE-INDUCING VIRUS IN STRAIN RIII MICE.

Smith GH, Andervont HB, Dunn TB
NCI, Bethesda, Md.
J Natl Cancer Inst; 44(3):657-671 1970

High-mammary tumor strain RIII mice, free of the mammary tumor virus (MTV) and designated RBR, were studied to see if they carried an agent similar to nodule-inducing virus (NIV), which is responsible for the appearance of spontaneous mammary tumors in C3Hf mice. After hybridization experiments were done between these mice and those of strains BALB/c (NIV-) and C3Hf (NIV+), mammary tumors that developed in these hybrids and in MTV-free RBR females were studied by electron microscopy to detect the presence of NIV. It is concluded that the RIII mice did not have an MTV variant similar to the NIV of C3Hf mice. A relationship between the many intracisternal type A particles noted in their tumors and in tumors of reciprocal RBR x BALB/c hybrids and MTV gene action is suggested.

294. PLASMA LEVELS OF A VIRAL PROTEIN AS A DIAGNOSTIC SIGNAL FOR THE PRESENCE OF MAMMARY TUMOR: THE EFFECT OF TUMOR REMOVAL.

Ritzi E, Martin DS, Stolfi RL, Spiegelman S
Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY 10032
J Exp Med; 145(4):999-1013 1977

Plasma concentrations of the 52,000 dalton glycoprotein (gp52) of murine mammary tumor virus (MMTV) were measured before and after resection of spontaneous mammary tumors in (BALB/c X DBA/8)F1 mice. The study demonstrated that the tumor is the principle source of the plasma gp52 since the levels of gp52 decreased 10-to 100-fold within 9 days of tumor excision. All tumor recurrences were correctly diagnosed by increases in gp52 levels; some were detected 4-7 days before they were found by palpation. The only animals that remained tumor-free at the end of the 106-day experiment were those who maintained a gp52 level of 15 nanog/ml or less. Plasma gp52 levels at the time of surgery were superior to tumor loads as prognostic indicators. The results support the feasibility of using plasma concentrations of viral proteins to assess the presence and status of a solid tumor. (9 Refs)

295. MAMMARY TUMORIGENESIS THROUGH IRRADIATION OF MICE.

Warren S, Gates O
New England Deaconess Hosp., Boston, Mass.
Radiat Res; 57(3):488-507 1974

RAP mice, possibly harboring mammary tumor virus, of representative ages were exposed to limited or life-time whole-body continuous gamma and to fractionated x-irradiation. Doses varied from 30-2100 R and dose rates from 0.062-121R/day in the 2 series GA (ambient) and PN (perinatal) in which mammary cancer incidence was elevated. Induction of mammary cancer was related to the dose range for ovarian tumorigenesis, 30-500R, but unrelated to age when exposed. There was no statistically significant correlation between mammary cancer and ovarian tumors. Active mammary tumor virus infection was suggested by cancer-prone litters in one irradiated (PN U + SR) and one unirradiated series (OCB). Unirradiated descendents of perinatally irradiated mice with an inherited hormonal disorder had a lower incidence of mammary cancer than stock virgin mice. The data obtained in this study indicate that the induction of mammary cancer results from the interaction of many factors through systemic changes set in motion by irradiation.

296. INHIBITION OF GROWTH OF MOUSE MAMMARY CARCINOMA BY STREPTOVARICIN (MEETING ABSTRACT).

Kramarsky B, Manthey WJ
Inst. Med. Res., Camden, N.J.
Proc Soc Exp Biol Med; 145(4):1434-1438 1974

Growth of existing mammary adenocarcinomas was inhibited 51% in MTV-positive RIII mice treated with streptovaricin (approx. 0.025 g/d, po, dietary) over 5 wk, and tumor growth increased rapidly after discontinuation of treatment. When treatment was continued until death, the reduction in growth rate was 87%, and 3/9 were tumor-free. Only 2 new tumors arose in treated animals, compared to 9 in the controls. Among animals treated for 5 wk, 25% survived at least 15 wk, while all control animals were dead at 12 wk. Among animals treated until death, 44% survived at least 15 wk, while only 11% of controls survived that period. No significant wt change occurred in tumor-free animals receiving the antibiotic complex. Prophylactic treatment of MTV-negative C57BL mice with streptovaricin failed to give significant protection against infection with MTV. (10 refs)

297. EFFECTS OF VARIOUS ONCOGENIC AGENTS ON TUMOR-PRODUCING CAPABILITIES OF SERIES D BALB/C MAMMARY NODULE OUTGROWTH LINES.

Medina D, DeOme KB
Baylor Coll. Med., Houston, Tex.
J Natl Cancer Inst; 45(2):353-363 1970

The effects of various oncogenic agents (mammary tumor virus, nodule-inducing virus, 3-methylcholanthrene and pituitary isografts) on the tumor-producing capabilities of nodule outgrowth lines D1, D2, D3, D4, D5, D7 and D8 was investigated in BALB/c mice. Fifty percent of the transplants produced tumors in 308, 182, 161, 238, 364 and 168 days in D1, D2, D2a, D3, D4 and D8 lines, resp. Mammary tumor virus infection increased the incidence of mammary tumors and decreased the mean latent period as compared to the same outgrowths transplanted into mammary tumor virus-free BALB/c mice, except for D5. Nodule-inducing virus showed some effect on the tumor potential of line D3 but not of line D3. 3-Methylcholanthrene increased the tumor potential of outgrowth lines D2 and D3 (45% and 60%, resp); pituitary isografts increased the tumor potential of line D2 (12%). The D series of nodule outgrowth lines appears to show a wide variety of responsiveness to various viral and chemical oncogenic agents and responses cannot be predicted from their background tumor potential.

298. CARCINOGEN-INDUCED MAMMARY TUMORS FROM PRENEOPLASTIC NODULE OUTGROWTHS IN BALB/C MICE.

Medina D, DeOme KB
Baylor Coll. Med., Houston, Tex.
Cancer Res; 30(4):1055-1059 1970

The effects of urethan (U; 0.2 ml of a 10% soln, 1 inj./week x 10 weeks, ip), 7,12-dimethylbenzanthracene (DMBA; 0.2 ml of a 0.25% soln, 1 admin./week x 3 weeks, po) and gamma-irradiation (450 r) on the tumor-production of mammary tumor virus (MTV)-negative, nodule-inducing virus-negative, D series of BALB/c nodule outgrowth lines D1 and D2 were studied. All 3 agents increased tumor-producing capabilities of D1, and gamma-irradiation did so in D2. (U and DMBA were not tested on D2). D1 treated with U or DMBA produced 45/59 (76%) and 16/25 (64%) tumors, resp, whereas irradiation produced 8/36 (22%) tumors and the untreated D1 had 1/74 (4%) tumors. Irradiation of outgrowth line D2 produced 61% tumors, compared to 14% tumors in untreated D2 controls. No MTV activity was found in blood from U- or DMBA-treated mice or in cell-free extracts of tumors arising in carcinogen-treated outgrowths. Neither Type A nor B virus particles were found in thin sections of carcinogen-treated outgrowths or tumors derived from carcinogen-treated outgrowths examined by electron microscopy.

299. MAMMARY TUMORS IN STRAINS BL/LYDE AND SWR/LYDE MICE.

Deringer MK
Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.
J Natl Cancer Inst; 45(2):215-218 1970

The presence of mammary tumor virus was demonstrated in strain BL/LyDe mice by the induction of mammary tumors in agent-free substrains C3Hf/HeDe and C3HeB/De mice foster-nursed by BL/LyDe mice. The incidence of mammary tumors in breeding females of strain BL/LyDe was 10% at an average age of death of 15.5 months, while the incidence of mammary tumors in foster-nursed females of strains C3Hf/HeDe and C3HeB/De at an average age of 18 months was 47% (controls, 2% and 4%). The types of mammary tumors produced were adenocarcinomas Type A and Type B. The incidence of mammary tumors in C3Hf/HeDe and C3HeB/De foster-nursed by SWR/LyDe females was 4% at an average age of death of 25 months, indicating that strain SWR/Lyde mice either do not possess mammary tumor virus or do not transmit it to foster-nursed animals.

300. MAMMARY TUMOR VIRUS IN STRAIN GR MICE IN RELATION TO AGE AND TISSUE TYPE.

Shannon JM, Aidells BD, Daniel CW
Cancer Res. Lab., U. California, Berkeley
J Natl Cancer Inst; 52(4):1157-1160 1974

Normal and neoplastic mammary tissues of GR/Crgl mice were examined for the presence of mammary tumor virions. Detection of both B and cytoplasmic A particles in normal glands from mice 2 wk of age and older was the earliest reported occurrence of such particles. Virus particles were not found in normal tissue from mice 24 wk or 1 wk old. All neoplastic tissues examined had moderate or abundant virus particles. The possible relationship of these findings to the mode of viral transmission in GR mice is discussed. A portion of the latent period observed in other mammary tumor virus-infected strains, during which mature virions cannot be observed in the mammary gland, may be consigned in GR to prenatal life. Therefore, the early viral infection of GR mice and the early development of virions in normal mammary

glands may be related to the early appearance of neoplastic lesions in this strain.

301. SPONTANEOUS KIDNEY TUMORS IN A SUBSTRAIN OF RIII/DM/SE MICE.

Ribacchi R
Lav Ist Anat Istol Patol (Perugia); 30(2):73-88 1970

The occurrence of 7 multiple nodular transplantable spontaneous kidney tumors of tubular epithelial origin was observed through 50 generations (a total of 5300 animals) of 3 substrains (A, B, C) of RIII/Dm/Se inbred mice. The mice were maintained on a normal pellet diet. The first kidney tumor occurred in a male of the 40th inbred generation of the A substrain and 6 kidney tumors occurred in 5 males and 1 female (bearing a minor mammary tumor) in 3 consecutive generations of the B substrain (1 in the 43rd, 2 in the 44th and 3 in the 45th, the latter occurring in descendents of the brood in which the first tumor occurred) at 548-599 days of age. No mouse of the C substrain developed kidney tumors. The incidence of kidney tumors throughout the 3 mentioned generations in the B substrain was 50% (5 out of 10 animals) in males and 10% (1 out of 10) in females, while the other 90% of females developed mammary tumors at an average age of 455 days. The incidence of mammary gland tumors in 3 groups of generations of the B substrain (females of the 36- 42nd, 43-45th and 46-49th generations) was 44% (12 out of 27), resp, and occurred at the average age of 434, 455 and 332 days, resp, indicating that a weakening of the MTV potency occurred in the generations preceding the appearance of the kidney tumors. The C breeders exhibited the highest incidence of mammary tumors (94% occurring at an average age of 266 days through the 36-49th generations) while the B breeders had the lowest incidence (69% occurring at the average age of 402 days). The development of kidney tumors seemed to be determined by chromosomal and/or extrachromosomal factors interfering with the transmission of the potency of the MTV.

B. Growth Control Studies of Transplanted Mammary Tumors

302. SERIAL TRANSPLANTATION OF URETHAN-TREATED MAMMARY NODULE OUTGROWTH LINE D1.

Medina D
Dept. Zool. Cancer Res. Genetics Lab., U. California, Berkeley
J Natl Cancer Inst; 48(5):1371-1375 1972

Urethan -treated mammary nodule outgrowths were serially transplanted in various groups of mice for two or more generations. The urethan-treated outgrowths differed from methylcholanthrene (MCA)-treated outgrowths in two ways: 1) D1 nodule outgrowths exposed to urethan produced a high incidence of tumors (83%) if left in situ, continuing to yield tumors (32%) when retransplanted into untreated mice. However, the tumor incidence decreases with successive transplant generations. 2) Urethan treatment did not alter the sensitivity of the nodule cells to hormone -mediated tumorigenesis. The oncogenic agents, urethan and mammary tumor virus (MTV), and urethan and MCA, were applied sequentially to D1 outgrowths. The results indicated that the effects of urethan and MTV, and urethan and MCA, were additive in the induction of mammary tumors. Thus, prior exposure of the outgrowths to urethan did not alter their responsiveness to MTV or MCA. These experiments provide no evidence that urethan interacts with MTV to promote mammary tumorigenesis in these nodule outgrowths.

303. NEOVASCULARIZATION INDUCED BY INTRAOCULAR XENOGRAFTS OF NORMAL, PRENEOPLASTIC, AND NEOPLASTIC MOUSE MAMMARY TISSUES.

Gimbrone MA, Gullino PM
Natl. Cancer Inst., U.S. Dept. Health, Education and Welfare, Bethesda, MD 20014
J Natl Cancer Inst; 56(2):805-818 1976

The capacity to induce neovascularization was compared in normal, preneoplastic, and neoplastic mouse mammary tumors from strains with a high incidence of tumors (C3H, C3H-Avy, C3H-AvyfB) by implantation of small biopsy fragments on the iris surface in New Zealand White rabbits. Proliferation of iris blood vessels was studied by: 1) direct, in vivo slitlamp stereomicroscopy and fluorescein angiography; 2) filling of the microvasculature with colloidal carbon; and 3) histologic examination. The microscopic anatomy of biopsy samples of normal mammary glands varied with the breeding history of the donor. Ninety percent of mammary tumor implants elicited iris neovascularization after 48-72 hours, regardless of their histologic classification or the presence or absence of mammary tumor virus. Corticosteroid treatment reduced immediate postoperative inflammation (12-36 hr) but did not abolish subsequent growth of new vessels. Necrotic tumor fragments failed to elicit any neovascular response. In contrast, only 6% of normal tissues from resting mammary glands caused any vasoproliferation. Hormone-stimulated mammary tissues from pregnant and lactating mice exhibited a transient neovascular capacity that was lost during postweaning involution. Of the implants from premalignant hyperplastic alveolar nodules (HAN's), 30% produced a pattern of vessel growth similar to that of tumor implants. D-1 line (HAN outgrowth) tissues, which have a predicted low incidence of tumors, induced significantly fewer neovascular responses than morphologically and biochemically similar D-2 line tissues, which have a predicted high incidence of tumors. These data suggest that the capacity to induce neovascularization is acquired during malignant progression of mouse mammary tissues; therefore, demonstration of this property may be useful in the identification of those intermediate populations most at risk for neoplastic transformation.

304. ANGIOGENIC CAPACITY OF PRENEOPLASTIC LESIONS OF THE MURINE MAMMARY GLAND AS A MARKER OF NEOPLASTIC TRANSFORMATION.

Gimbrone MA, Gullino PM
Department of Pathology, Peter Bent Brigham Hospital, Boston, Mass 02115
Cancer Res; 36(7):2611-2620 1976

The angiogenic capacity of normal, preneoplastic, and neoplastic murine mammary tissues from high-tumor-incidence strains (C3H, C3H-A**vy, C3H-A**vyfB) was compared by implanting small biopsies on the iris surface in New Zealand White rabbits. Proliferation of iris blood vessels was studied by: (a) in vivo slit-lamp stereomicroscopy and fluorescein angiography; (b) colloidal carbon injection of the microvasculature; and (c) histological examination. Ninety percent of mammary tumor implants elicited neovascular changes after 48 to 72 hr, regardless of their histological classification or the presence or absence of mammary tumor virus. Corticosteroid treatment did not abolish this response. In contrast, only 6% of implants from normal mammary glands caused any vasoproliferation. Thirty percent of implants from premalignant hyperplastic alveolar nodules produced a pattern of vessel growth similar to tumor implants. D-2 line (hyperplastic alveolar nodule outgrowth) tissues, which have a high predicted tumor incidence, induced significantly more neovascular responses (p less than 0.002) than do morphologically and biochemically similar D-1 line

tissues, which have a low predicted tumor incidence. These data suggest that angiogenic capacity is expressed during the malignant progression of murine mammary tissues; this property may provide a means for identifying those preneoplastic tissues that are most at risk for cancer. (Author Abstract)

305. HORMONE DEPENDENCE AND ESTRADIOL RECEPTORS IN THE D SERIES OF MAMMARY NODULE OUTGROWTH LINES AND TUMORS.

Medina D, Iramain CA, Clark JH
Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77025
Cancer Res; 35(9):2355-2360 1975

Preneoplastic mammary nodule outgrowth lines were examined for their ability to grow and produce tumors in ovariectomized BALB/c mice. In addition, these nodule outgrowth lines and tumors derived from them were investigated for cytoplasmic estrogen receptor proteins by qualitative and quantitative techniques. Early ovariectomy, performed within 4 weeks after transplantation, slightly delayed but did not permanently block the ability of three different nodule lines to completely fill the fat pad with nodule tissue. Ovariectomy performed later than 4 weeks after transplantation or adrenalectomy performed early or late had no effect on nodule growth. Neither early nor late ovariectomy or adrenalectomy had an effect on the maintenance of the nodule alveolar phenotype. Ovariectomy performed 3 weeks after transplantation had little effect on the tumor potential of the low oncogenic line D1 or the high oncogenic line D2. Samples of nodule outgrowths transplanted from ovariectomized mice responded to a chemical carcinogen in a similar manner, as did nodule outgrowths transplanted from control experiments. Thus, the altered hormonal environment in ovariectomized mice apparently did not select for subpopulations of nodule cells with altered tumorigenic potentials. The ovarian independence of the nodule lines and tumors derived from them was correlated with a very low level of cytoplasmic estrogen receptor. These results, along with other data, illustrate the nature of the independence on ovarian hormonal control for tumorigenesis in these mammary tumor virus-free nodule lines.

306. EFFECT OF HORMONE STIMULATION, DOSE, AND TIME OF ADMINISTRATION OF CARCINOGEN ON CARCINOGEN-INDUCED MAMMARY TUMORS FROM PRENEOPLASTIC NODULE OUTGROWTHS.

Medina D
Baylor Coll. Med., Houston, Tex.
J Natl Cancer Inst; 46(4):909-916 1971

The tumorigenic effects of 7,12-dimethylbenz(a)anthracene (DMBA) and urethan and of gamma-irradiation were analyzed on nodule outgrowth line D1, one of a series of BALB/c mouse mammary tumor virus-free outgrowths. DMBA and urethan treatment produced 68% and 83% tumor growth, whereas irradiated outgrowths produced only 23% tumor growths. Hormone stimulation (pituitary isograft) enhanced the effects of DMBA whereas hormone effects with urethan administration failed to show statistically different results and gamma-irradiation was inhibited in its ability to produce tumors. Time of administration and dosage determined the response of outgrowths to urethan; exposure at 3-5 wk after transplantation resulted in greatest incidence of outgrowth. Apparently the nature of the cell population exposed to the carcinogen determined the response of the outgrowths.

307. INFLUENCE OF MILK SOURCE ON TRANSPLANTABILITY OF HISTOCOMPATIBLE MAMMARY TUMOURS IN MICE.

Oth D, Sabolovic D
INSERM Res. Unit 95, Plateau de Brabois, 54500 Vandoeuvre, France
Br J Cancer; 35(6):752-760 1977

It is confirmed that C3H mammary tumors are much more easily transplantable in histocompatible recipients when these have been reared on C3H milk, than when they have been reared on milk from the inbred Swiss/B strain. By contrast, A.CA mammary tumors transplanted in histocompatible hosts reared on A.CA or Swiss/B milk, grow almost equally well in both sorts of recipient. Thus, rearing on Swiss/B milk has different effects on the transplantability of mammary tumors of C3H and A.CA. On the other hand, recipients which were reared on C3H or A.CA milks accept grafts of C3H mammary tumors about equally, suggesting that milks from A.CA and C3H have the same effect on the transplantability of C3H mammary tumors. The different action of Swiss/B milk on tumors of C3H and A.CA seems best attributed to differences between C3H and A.CA tumors or between mouse strain genotypes. By contrast, the transplantability of C3H mammary tumors was significantly changed when the recipients were reared on milk from the RIII strain instead of C3H. These facts suggest that the milk from RIII has an action which differs from that of both C3H and A.CA in this respect. The data are discussed on the basis of a differential tolerance-inducing action of mammary tumor viruses (MTVs) which infect C3H, A.CA and RIII, and have an important role in tumor induction. (Author abstract) (13 Refs)

308. PREGNANCY DEPENDENCE OF MAMMARY TUMORS IN STRAIN DDD MICE.

Matsuzawa A, Yamamoto T, Suzuki K
Inst. Med. Sci., U. Tokyo, Japan
J Natl Cancer Inst; 52(3):449-456 1974

Mammary tumors, which developed in 22 of 2411 strain DDD retired breeder mice under 12 months of age, were transplanted into virgins. Half the recipients were bred so that the tumors could be examined for pregnancy dependence: four were classified as completely pregnancy-dependent (CPD), two as moderately pregnancy-dependent (MPD), three as slightly pregnancy-dependent (SPD), and 13 as pregnancy-independent (PID). The CPD tumors did not grow in virgins but grew rapidly in pregnant breeders and regressed after parturition, reaching ascending peaks in successive pregnancies. Morphologically, all CPD tumors were classified as type A. One MPD tumor was type A and the other, a pale-cell carcinoma. Two type A+B and 1 type P were SPD. PID tumors consisted of three type A + B, five type P, three pale-cell carcinomas, and two mixed tumors. These findings suggest that the mammary tumor virus (MTV) of strain DDD may belong to plaque-forming mammary tumor virus.

309. TUMORIGENICITY AND ISOIMMUNIZING PROPERTIES OF C3H MOUSE CELLS UNDERGOING "SPONTANEOUS" MALIGNANT CONVERSION IN VITRO.

Kieler J, Radzikowski C, Moore J, Ulrich K
Fibiger Lab., Copenhagen, Denmark
J Natl Cancer Inst; 48(2):393-405 1972

Three C3H mouse cell lines, derived from embryo, spleen and lung, showed spontaneous malignant transformation in vitro. Cells of these transformed lines were injected into C3H and other mice to test for tumorigenicity and to determine whether such injections immunized against transplants of the same cells. The cytotoxicity in vitro of sera and lymphoid cells

from mice injected with transformed cells was also observed. Transformed cells were tumorigenic; newborn mice were more susceptible than adults. Transformed cells developed isoimmunizing properties, as evidenced by in vivo transplantation immunity tests and by in vitro cytotoxicity tests with sera and lymphoid cells. Earle's L-929 mouse fibroblasts, the three cell lines which transformed spontaneously plus another such line, and four tumors derived from these cell cultures induced immune cross-reactions in C3H mice in transplantation experiments. Cross-reactions were also seen between the three principal cell lines studied and their corresponding antisera in vitro. There was no evidence that the development of common antigenic properties was due to murine leukemia virus, mammary tumor virus, or mycoplasma. Tumors derived from the three cell lines were transplantable into allogeneic hosts, even when hosts were immunized with normal C3H cells, indicating that the appearance of "tumor-associated" isoantigens was followed by the loss or dilution of normal H-2 antigens.

310. EFFECT OF EARLY THYMECTOMY ON GROWTH OF TRANSPLANTED MAMMARY GLAND TUMORS ARISING IN C3HF MICE.

Videlets IY
Inst. Cytology and Genetics, Acad. Sciences USSR, Siberian Branch, Novosibirsk, USSR
Exp Biol Med; 81(6):896-898 1976

The influence of early thymectomy on the growth of transplanted mammary gland tumors arising in C3Hf mice is studied. Mice of the C3H/He strain or (C3H/He x C57BL)F1 hybrids were used as the MTV-S+ animals and C3Hf or (C57BL x C3H/He)F1 hybrids as the MTV-S- group. Three tumors arising spontaneously in a colony of C3Hf mice were utilized: OMZhf-2, OMZhf-3, and OMZhf-4. The MTV-S+ and MTV-S- mice were inoculated simultaneously with 0.2 ml of a 10% suspension of tumor cells sc in the dorsal region. No significant differences were found between the av wt of the tumor in the MTV-S+ and MTV-S- recipients, but after transplantation of the OMZhf-2 tumor a significantly higher percentage of transplanted tumors was observed in the C3Hf mice than in the C3H/He mice. In the case of the other two tumors, no significant differences were found in the percentage of successfully transplanted tumors or in the duration of the av latent period between the MTV-S+ or S- recipients. Infection of the recipients at an early age with Bittner virus did not lead to more rapid growth of the transplanted tumors arising in the MTV-S- mice. Experiments were carried out on C3H/He and C3Hf mice. The experimental animals were thymectomized on day 6 after birth. At the age of 3 mo, the mice were inoculated with 0.2 ml of a 10% suspension of OMZhf-2 or OMZhf-4 tumor cells sc in the dorsal region. Early thymectomy on C3H/He (MTV-S+) mice had no inhibitory action on the rate of growth of the transplanted mammary gland tumors arising in MTV-S- mice of the C3Hf strain. In C3Hf(S-) mice, early thymectomy likewise did not affect the rate of growth of the transplanted S- tumor of the C3Hf mice. The results indicate that the more rapid growth of the tumor in the MTV-S+ mice and its delay after early thymectomy are connected with the immunological response to virus-induced antigens. (11 Refs)

311. TARGET ORGAN FOR A SYSTEMIC EFFECT OF ULTRAVIOLET RADIATION.

Kripke ML
NCI Frederick Cancer Res. Center, Frederick, MD 21701
Photochem Photobiol; 24(6):599-600 1976

C3H/HeN(MTV-) mice, a strain of specific pathogen-free mice, were used to demonstrate that the suppression of resistance to UV-induced tumor growth is mediated via the skin. Irradiation was by six Westinghouse sunlamps, 1 hr, 3X per wk. Unshaven and shaven (dorsal side) mice received 8 or 14 wk of UV radiation prior to challenge by a fibrosarcoma tumor previously induced by UV irradiation in a C3H/HeN(MTV) mouse. Tumors were transplanted on the ventral non-irradiated side. Nine of 10 untreated control mice rejected the transplanted tumors; shaved irradiated mice were highly susceptible (10 tumors/10 mice at 8 wk). A shielding effect of hair was seen after 8 wk of UV treatment; among unshaven mice, only 5/10 mice developed tumors. However, by the 14th wk, 9/10 unshaven mice had tumors. Another group of mice were subjected to enucleation; 10/10 of these blind mice developed tumors after irradiation. None of the 10 nonirradiated enucleated mice developed tumors. (1 Refs)

312. EFFECT OF ERGOCORNINE ON TRANSPLANTED MAMMARY TUMOR GROWTH AND PITUITARY PROLACTIN LEVEL IN BALB/C MICE.

Singh DV, Meites J, Halmi L, Kortright KH, Brennan MJ
Detroit Inst. Cancer Res., Detroit, Mich.
J Natl Cancer Inst; 48(6):1727-1731 1972

Inj of ergocornine in mice with transplanted D2-mammary tumors decreased tumor growth; the decrease was associated with reduced pituitary prolactin levels. Virgin, 8- to 10-wk-old female BALB/c mice, free of mammary tumor virus, received sc transplants of D2-mammary tumors. Five wk after transplantation, the animals were divided into a control group that received the inj vehicle (ethanol-saline) and an experimental group that received sc inj of ergocornine (wk. 1, 20 microg; wk. 2-4, 50 microg; wk. 5, 100 microg). At the end of 5 wk, half the animals in each group were sacrificed. In the sacrificed control group (I), mean tumor diameter (MTD) had increased from 17.0 mm to 31.0 mm (82%; p less than 0.001); in the sacrificed experimental group (II), MTD had increased from 19.9 mm to 21.0 mm (9.5%; not significant). At the end of 5 wk, MTD of control group I was 48% greater than that of the treated group II. Continued comparison of MTD in control (III) and treated (IV) mice in which treatment was discontinued at 5 wk. (but the animals not sacrificed) showed a small (29%) growth increment of MTD in group III 4 wk after the treatment regimen was discontinued, whereas group IV mice had a dramatic (44%) increase in MTD by the end of the 1st wk and a 100% increase 4 wk after termination. Mean tumor wt. (MTW) in group I was greater than in group II by 29% at the end of treatment. In group III, final MTW (4 wk after treatment stopped) was 13% lower than in group IV. Ovaries of treated mice were slightly heavier than those of control mice, although treatments had no significant effect on ovarian wt. Mean adrenal wt in group II was 14% lower than in group I at the end of treatment; 4 wk after termination of treatment, adrenal wt in group IV was 13% greater than in group III. Mean anterior pituitary prolactin content in group I animals at the end of 5 wk was not significantly different from content in group III animals 5 wk after inj were terminated. Group II animals showed a marked fall in these levels of pituitary prolactin as compared to group I, but the difference disappeared in group IV. Ergocornine significantly reduced these levels during treatment. (28 refs)

313. CELL RECOGNITION BY MALIGNANT MAMMARY EPITHELIUM (MEETING ABSTRACT).

Pitelka DR
Dept. Zoology and Cancer Res. Lab., Univ. California, Berkeley, CA 94720
J Cell Biol ; 70(2/Part2):5a 1976

Mammary tumors in mice infected with mammary tumor virus occasionally invade the underlying body wall and frequently metastasize to the lung. The pattern of invasion is being investigated by light and electron microscope study of the interface between the tumor and other tissues. The expanding tumor mass may penetrate the body-wall muscle layer and bulge into the peritoneal cavity; in all cases seen,

normal or hypertrophied basal lamina is maintained between the tumor epithelium and surrounding muscle, connective tissue, or peritoneal mesothelium. In the lung, the earliest metastatic foci observed are within arterioles, where the malignant mammary cells proliferate until the cellular and elastic layers of the vessel wall rupture, permitting the tumor to expand into the pulmonary connective tissue and ultimately to invade the air spaces. Within the arteriole, normal or hypertrophied basal lamina is present between mammary epithelium and the vascular endothelial lining. The basal lamina continues to surround the growing mass in the pulmonary connective tissue. Entry into air spaces appears to be achieved by local fusion of the tumor's basal lamina with that of the alveolar epithelium, followed by disruption of the fused zone. Once in contact, pulmonary epithelial cells and mammary epithelial cells mingle freely, with no intervening lamina; tumor cells even abut on alveolar lumina, forming tight junctions with pulmonary cells. Malignant mammary pulmonary cells thus appear to recognize each other as epithelial, whereas the malignant mammary cells separate themselves by basal laminae from both vascular endothelium and peritoneal mesothelium, as well as from connective tissue and muscle.

314. A SOLID TUMOR ANIMAL MODEL PREDICTIVE FOR HUMAN BREAST CANCER.

Martin DS, Fugmann RA, Stolfi RL, Hayworth PE
Catholic Medical Center, Woodhaven, N.Y. 11421
Proc Am Assoc Cancer Res; 16:175 1975

Data on a spontaneous (MTV+), murine (CD8F1) mammary tumor demonstrates a pre-clinical predictive tool to investigate drug scheduling, immunotherapy, combination chemotherapy and combined modality therapy for human breast cancer. The tumor-host system can be studied in different forms: 24 hour 1st generation transplants in either sex, slow-growing advanced tumor transplants, a metastases model, and in the autochthonous situation. Eleven of twelve clinically positive agents against human breast cancer (list selected by NCI) are active against the animal tumor. As in the clinical situation, surgical adjuvant chemotherapy with either the triple combination of Cytoxan (C) + Adriamycin (A) + 5-Flourouracil (F) or Phenylalanine Mustard + A + F is more effective than any lesser combination or single agent above. Immunological parameters concerning host and the autochthonous tumor can be evaluated and are critical in scheduling agents for cure, as will be demonstrated with immuno-chemotherapy data (employing a non-specific immunostimulant and combination chemotherapy against the autochthonous tumor). Further, it seems likely that this slow-growing tumor model should also reveal information of value for human solid tumors other than breast. (Author Abstract)

315. CELL DENSITY-DEPENDENT GROWTH IN AGAR OF BONE MARROW CELLS FROM TUMOR-BEARING BALB/C MICE IN THE ABSENCE OF A COLONY-STIMULATING FACTOR.

Nooter K, Bentvelzen P
Radiobiol. Inst. Rijswijk, Netherlands
Cancer Res; 35(1):117-121 1975

The ability of bone marrow from BALB/c mice with various types of tumors to grow in agar in the absence of colony-stimulating factor (CSF) was studied. Bone marrow cells from female mice with Rauscher murine leukemia virus (RLV)-induced erythroblastosis, myeloid leukemia and lymphosarcoma, and with murine mammary tumor virus (MTV)-induced mammary tumors were added to agar in the presence and absence of CSF. Bone marrow cells from mice with myeloid leukemia, lymphosarcoma, erythroblastosis, or mammary tumor produced small clusters in the semisolid agar cultures in the absence of specific CSF. This spontaneous growth was observed only when high cell numbers (5 x 105 cells/ml) were plated, and the phenomenon was encountered only when the mice had an elevated number of mature or immature granulocytes in the peripheral blood. Removal of the adherent cells from the bone marrow did not abolish the spontaneous growth, indicating that this CSF independency was not due to a high number of colony-stimulating cells in the bone marrow of the cancerous mice. Feeder layers of bone marrow cells from the diseased animals had no higher colony-stimulating activity than did normal bone marrow cells, which excluded the possibility that the spontaneous growth was due to a high endogenous stimulating activity of the bone marrow from the tumor-bearing mice. The active effect of closely packed cells at high cell densities may be the factor which generates some growth in the case of diseased animals.

316. PRENEOPLASTIC LESIONS IN MURINE MAMMARY CANCER.

Medina D
Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030
Cancer Res; 36(7):2589-2595 1976

The current model for murine mammary tumorigenesis indicates that discrete, morphologically identifiable preneoplastic lesions precede and give rise to mammary tumors. The hyperplastic alveolar nodule is the primary lesion that precedes and gives rise to mammary tumors in mice infected with the mammary tumor virus (Bittner) or its variants. In mice fed 7,12-dimethylbenzanthracene or urethan, hyperplastic alveolar nodules are present but infrequent, and the major mammary dysplasias present are ductal hyperplasias. The ductal hyperplasias can be divided into four general morphological types: (a) simple terminal duct hyperplasia; (b) lobular hyperplasia; (c) papillary hyperplasia; (d) end-bud hyperplasia. All types of ductal hyperplasias are characterized by intraductal epithelial hyperplasia and have been shown to give rise to mammary adenocarcinomas in situ or by transplantation into the mammary gland-free fat pads of syngeneic mice. Our current hypothesis is that murine mammary cancer can evolve through one of several intermediate stages. The intermediate stages can be either alveolar or ductal hyperplasias. The latter resemble, in many instances, ductal lesions seen in human breast cancer. (Author Abstract)

VII. STUDIES ON THE ASSOCIATION OF THE MuMTV AND HUMAN CANCER

A. MuMTV and Human Cancer: Nucleic Acid Studies

317. MOUSE MAMMARY TUMOR VIRUS RELATED RNA IN HUMAN TUMORS (MEETING ABSTRACT).

Vaidya AB, Dion AS, Black MM, Moore DH
Inst. Med. Res., Camden, N.J.
Proc Am Assoc Cancer Res; 15:95 1974

Carefully selected histological types of human breast tumors were probed for MuMTV related nucleic acids by molecular hyoridization techniques. Single-strand specific nuclease S1 from Aspergillus was used to detect and quantitate hybrid formation between nucleic acids isolated from human tumors and single-stranded DNA synthesized from MuMTV. Out of 15 human tumors tested so far, 5 had RNAs which hybridized from 20 to 77% of MuMTV DNA probes at Crt values greater than 10^4. Estimations from Crt curves indicated a low number of MuMTV related RNA molecules per cell. Also, about 5% mismatching was detected in these hybrids by thermal stability experiments. The results obtained are very similar to those reported recently for MuMTV-non-producing murine tissues.

318. HOMOLOGY BETWEEN HUMAN BREAST TUMOUR RNA AND MOUSE MAMMARY TUMOUR VIRUS GENOME.

Vaidya AB, Black MM, Dion AS, Moore DH
Inst. Med. Res., Camden, N. J.
Nature (Lond); 249(5457):565-567 1974

Hybridization experiments were carried out using mouse mammary tumor virus (MuMTV)-specific DNA probes and human breast tumor RNA. Out of 17 tumors tested, five had RNA sequences homologous to the MuMTV genome. When a DNA probe synthesized by Mason-Pfizer monkey virus (MPMV) was used for hybridization under the same conditions, none of the tumors tested showed any RNA sequences homologous to the MPMV genome. All five positive human tumor RNAs showed varied rates of hybridization with the MuMTV DNA probe. The numbers of MuMTV related RNA molecules per cell in the human tumors ranged from 1.5 to 8. With regard to thermal stability, the Tm for hybrids of MuMTV DNA and RNA from RIII lactating mammary gland (a tissue which produces MuMTV) was 69 C compared with 62 C for the hybrids of MuMTV DNA and human tumor RNA. This difference would indicate about 5% mismatching between the MuMTV DNA and the tumor RNA.

319. REPLICATION OF ONCORNAVIRUS-LIKE PARTICLE IN HUMAN BREAST CARCINOMA CELL LINE, MCF-7.

McGrath CM, Grant PM, Soule HD, Glancy T, Rich MA
Div. Biol. Sci., Michigan Cancer Found., Detroit
Nature (Lond); 252(5480):247-250 1974

The density distribution of RNA-containing particles released from MCF-7 human breast carcinoma cells during a 48-hr labeling period at 25 C showed a major particle population at 1.17 g/ml and a minor population at 1.23-1.25 g/ml. When the cells were labeled at 37 C, only the particles of density 1.23-1.25 g/ml were recovered. Four RNA populations were identified by gel electrophoresis in a particle population of density of 1.16-1.18 g/ml; the molecular weights of these RNAs ranged from 1 X 106-12 X 106 daltons. The major RNA species from the MCF-7 cells consistently displayed reverse transcriptase activity using endogenous RNA as template; the high molecular weight RNA served as template or primer in this reaction. About 15-20% of the total product consisted of RNA-DNA product was a hydrogen bonded heteroduplex. An antiserum against murine mammary tumor virus (MuMTV) reacted in indirect immunofluorescence tests with 5-7% of MCF-7 cells; the antiserum did not react with mouse cells infected with murine leukemia viruses (MuLV) or with non-particle-producing human cells. Absorption of the antiserum with MuMTV isopycnically banded from mouse milk markedly reduced its reactivity with MCF-7 cells. The MCF-7 particles appeared to be antigenically unrelated to MuLV.

320. PRESENCE IN HUMAN BREAST CANCER OF RNA HOMOLOGOUS TO MOUSE MAMMARY TUMOUR VIRUS RNA.

Axel R, Schlom J, Spiegelman S
Inst. Cancer Res., Coll. Phys. Surg., Columbia U., New York, NY
Nature (Lond); 235(5332):32-36 1972

Hybridization experiments were conducted using purified mouse mammary tumor virus (MMTV)-directed DNA and purified RNA from human breast neoplasms. DNA-RNA hybrids were detected by isopycnic separation in Cs2SO4 gradients. Six to 17% of MMTV 3H-DNA hybridized to RNA from human malignant breast tumors. Attempts to anneal MMTV-DNA to RNA from normal breast tissue or from fibrocystic disease tissue were unsuccessful. Of the 29 malignant breast tumors tested, 67% gave significantly positive responses. Hybridization of MMTV-DNA was specific for RNA from breast malignancies. No positive results were obtained with any human leukemias or sarcomas. Breast tumor RNA was likewise specific for MMTV-DNA; no annealing occurred with avian myeloblastosis virus-directed DNA.

321. HUMAN LEUKAEMIC CELLS CONTAIN TRANSCRIPTASE ASSOCIATED WITH A HIGH MOLECULAR WEIGHT VIRUS-RELATED RNA.

Baxt W, Hehlmann R, Spiegelman S
Coll. Phys. Surg., Columbia U., New York, N.Y.
Nature New Biol; 240:72-75 1972

Nuclei from peripheral white blood cells of leukemia patients were centrifuged and the supernatants were recentrifuged to isolate membranes and viral particles (if present). This material was used in a reverse transcriptase reaction. The products of the reaction often formed 70S complexes involving DNA from leukemic white blood cell material and a 70S RNA molecule. These complexes were formed by white blood cell material from 95% of 23 leukemia patients sampled. DNA from this 70S-DNA complex did not anneal to 70S RNA from murine mammary tumor virus or avian myeloblastosis virus. The DNA did hybridize with Rauscher leukemia virus RNA; 75% of leukemic DNA complexed to RLV RNA.

322. QUANTITATION OF RNA TUMOR VIRUSES AND VIRUS-LIKE PARTICLES IN HUMAN MILK BY HYBRIDIZATION TO POLYADENYLIC ACID SEQUENCES.

Schlom J, Colcher D, Spiegelman S, Gillespie S, Gillespie D
Coll. Physicians Surgeons, Columbia U., N.Y.
Science; 179(4074):696-698 1973

RNA tumor viruses and virus-like particles from human milk were quantitated by hybridization of the polyadenylic acid poly(A) regions in their 60-70S RNA to radioactive polyribouridylic acid of known specific activity. The poly(A) stretches in the 60-70S RNA from human milk particles were the same length, approximately 200 nucleotides long, as those found in the mouse mammary tumor virus and in other RNA tumor viruses. Five (14%) of 37 samples of human milk were positive for poly(A) regions, ranging in particle counts from 1.0 X 106 to 4.0 X 107 particles/ml. That 86% of the milks tested were negative indicated that the 14% positives were not due to normal RNA species of human lactating mammary tissue.

323. FURTHER EVIDENCE FOR ONCORNAVIRUSES IN HUMAN MILK: THE PRODUCTION OF CORES (MEETING ABSTRACT).

Feldman SP, Schlom J, Spiegelman S
Coll. Phys. Surg., Columbia U., New York, N. Y.
Proc Natl Acad Sci USA; 70(7):1976-1980 1973

A technique is described, using phospholipase C digestion followed by equilibrium density gradient centrifugation, for the preparation of cores, or nucleoids, from mouse mammary tumor virus and from human milk particles. Cores from both sources have a density of 1.26-1.27 g/ml and contain a 60-70 S RNA associated with an RNA-directed DNA polymerase. These results provide further evidence of similarity between human milk particles and animal RNA tumor viruses. Use of the "core-isolation" technique separates the cores from cell debris and associated enzymes which may inhibit RNA-directed DNA polymerase and thus mask the presence of virus.

324. EVIDENCE OF VIRAL INVOLVEMENT IN MURINE AND HUMAN MAMMARY ADENOCARCINOMA.

Schlom J, Spiegelman S
Coll. Physicians Surgeons, Columbia U., New York, N. Y.
Am J Clin Pathol; 60(1):44-56 1973

Particles which have several biochemical and biophysical properties diagnostic of ribonucleic acid (RNA) tumor viruses of animals have been isolated from specimens of human milk. The human particles have a density of 1.16 to 1.19 g per mo, a RNA-directed deoxyribonucleic acid polymerase, and a 60-70S RNA. The quantity of particles in particular milk samples is determined by hybridization of the polyadenylic acid regions of their 60-70S RNA to radioactive polyribouridylic acid of known specific activity. A method involving molecular hybridization with radioactive DNA complementary to the RNA of the mouse mammary tumor virus was used to detect homologous RNA in both murine and human malignant breast tumors.

325. DETECTION OF HIGH-MOLECULAR-WEIGHT RNA IN PARTICLES FROM HUMAN MILK.

Schlom J, Spiegelman S, Moore DH
Coll. Phys. Surg., Columbia U., New York, N. Y.
Science; 175(4021):542-544 1972

An assay developed to permit the simultaneous detection of reverse transcriptase and the 60S to 70S high-molecular-wt RNA unique to the oncogenic RNA viruses (oncornaviruses) was applied to particles isolated from human milk. Milk preparations were clarified by EDTA treatment and centrifugation. The pellet was suspended in NP40 and dithiothreitol and an endogenous reverse transcriptase reaction was carried out using 3H- TTP incorporation into DNA. The nucleic acids were then extracted and subjected to Cs2S04 equilibrium gradient centrifugation. Fractions were collected and analyzed for acid-insoluble radioactive material. Under these conditions, the presence of 3H-DNA which sedimented as 60S-70S material indicated the presence of both reverse transcriptase and 60S-70S RNA. Numerous preparations of human milks were assayed and RNA:3H-DNA complexes were observed sedimenting at 67S. One milk preparation from a woman with a family history of breast cancer showed an excessively high peak of radioactivity in the 60S to 70S region. Milks from different women varied in enzyme content and milks from individual women differed from day to day. These effects could be due either to actual variation in the amounts of milk particles or to the variable presence of inhibitors. Inhibitors were implicated in at least one case in which no 3H- DNA:RNA 60S to 70S complex was observed when RIII mouse milk containing mouse mammary tumor virus (MMTV) was mixed with human milk. RIII milk processed alone produced such a complex. 3H- DNA in the 35S region was also found in assayed milks from nine of 20 women. A similar 35S complex has been observed in the assay of MMTV and other oncogenic RNA viruses.

326. METHODS FOR DETECTION OF ONC-ORNAVIRUSES IN HUMAN TUMORS. (PP. 221-223)

Steinke H, Laufs R, Dorfler W
Molecular Base of Malignancy, New Clinical and Therapeutic Evidence. Deutsch E, Moser K, Rainer H, Stacher A, ed. Stuttgart, Georg Thieme Publishers, 1976.

Methods to detect oncornaviruses in tumor tissue, especially those that do not depend on completely expressed type C viruses, are of great diagnostic interest. One such method, the simultaneous detection test for RNA-instructed DNA polymerase and high molecular wt (70S) RNA (two diagnostic features of RNA tumor viruses), was used to examine tumorous spleens from BALB/c mice infected with Rauscher leukemia virus (RLV), tissue from C3H mice infected with mouse mammary tumor virus (MMTV), and NC-37 cells carrying simian sarcoma virus type 1 (SSV-1). The presence of RNA-instructed ^{3}H-DNA was analyzed in a glycerol sedimentation velocity gradient. Mouse tumors induced with RLV and MMTV resulted in a distinct peak of acid-precipitable ^{3}H-TTP with a sedimentation coefficient of 70S; this peak represents complexes that contain 70S RNA molecules. The ^{3}H-DNA product obtained from NC-37 cells infected with SSV-1 was precipitated with ethanol and analyzed on a Cs2 SO4 gradient. Part of the product banded in the RNA region. Complexes of ^{3}H-DNA and RNA obtained in the 70S region from the NC-37 cells were precipitated with two volumes of ethanol in the presence of 0.2 M NaCl at -20 C for 12 hr and treated with 0.5 M NaOH at room temperature for 4 hr to hydrolyze any RNA present. The radioactive DNA banded solely in the DNA region. Annealing reactions between ^{3}H-DNA of SSV-1 (1,000 to 2,000 cpm) and RNA from polysomes of cells infected with SSV-1 (300 ug) were performed in 0.4 M NaCl-50% formamide-50% 5 mM EDTA at 37 C for 24 hr. About 40% of the input ^{3}H-DNA from SSV-1 hybridized to the polysomal RNA from the NC-37 cells. A lacking partial expression of an oncornavirus genome does not rule out a silent oncornavirus genome in the tumors.

327. MOLECULAR EVIDENCE FOR VIRAL AGENTS IN HUMAN CANCER AND ITS CHEMOTHERAPEUTIC CONSEQUENCES.

Spiegelman S
Inst. Cancer Res. Coll. Phys. Surg., Columbia Univ., New York,
Cancer Chemother Rep; 58(4):595-613 1974

Sequence homology between virus and cellular nucleic acids was studied. Homology exists between myeloblastosis and Rous sarcoma virus (RSV), and between murine leukemia and murine sarcoma viruses (MuLV, MuSV, respectively), although murine mammary tumor virus (MMTV) was unique. Human tumor cells were examined by DNA/RNA hybridization technics, using viral-specific labeled DNA. Homologies were found between human mammary and MMTV nucleic acids and between human leukemia, lymphoma, and sarcoma and RLV nucleic acid. The cytoplasmic RNA from 21 patient with Burkitt's lymphoma contained sequences homologous with RLV in 76% of cases, but there was no homology with MMTV. A simultaneous detection test for high molecular wt viral RNA and reverse transcriptase was described. The application of this test to 38 patient with adenocarcinomas gave 74% positive results, yielding an RNA density characteristic of oncogenic viruses. The peripheral leukocytes of 23 leukemic patient contained virus-like particles in over 95% of cases, although none of 18 non-leukemic controls contained these particles. In 70% of Hodgkin's disease patient, 82% with Burkitt's lymphoma, and 88% of patient with other cancers (including lymphosarcomas and reticulum cell sarcomas), these virus-like particles were detected. The virus-like particles had a buoyant density of 1.16-1.19 g/ml, and contained 70S RNA associated with reverse transcriptase. The malignancy DNA was shown to be absent from the germ lines of normal human cells, and normal DNA did not complex with lymphoma ^{3}H-DNA. The DNA from 2 leukemic identical twin pairs contained 70S particles homologous with virus-like material but absent in the cells of their normal healthy twins. Hence, the malignant transformation requires the insertion of viral-related information, and raises the possibility of pre-disease clinical diagnosis by hybridization technic. (33 refs)

328. HUMAN CANCER AND ANIMAL VIRUS ONCOLOGY.

Spiegelman S, Axel R, Baxt W, Kufe D, Schlom J
Coll. Physicians Surg., Columbia U., New York, N. Y.
Cancer; 34(4):1406-1420 1974

DNA-RNA hybridization was used to determine whether human neoplasias contain RNA molecules having sequence homologies to those of the RNA tumor viruses known to cause similar diseases in animals. The pattern of specific RNAs found in the human tumors showed a remarkable concordance with the predictions deducible from the animal systems. Thus human breast cancer contains RNA homologous only to that of the murine mammary tumor virus (MMTV). Human leukemias, sarcomas, and lymphomas (including Hodgkin's and Burkitt's) all contain RNA with sequence homology to the murine leukemia virus (RLV) and not to MMTV RNA. Finally, as in the case of the mouse, none of the human tumors examined contained RNA related in sequence to that of the avian myeloblastosis virus. The RNA detected in all of the human neoplasias was of high molecular weight (1 X 107 daltons) and encapsulated with a reverse transcriptase in particles having densities between 1.16-1.19 g/ml. Further, the RNA of these human tumor particles was related in sequence to the murine viruses that cause the corresponding neoplasias in mice. Thus, four features diagnostic for the murine oncogenic viruses are satisfied by the particles found in the human cancers. Finally, "recycling" experiments showed that the DNA from human leukemic cells and lymphomatous tissue contained particle-related sequences not detectable in normal DNA. This finding was further substantiated by studies with identical twins, in which it was shown that the leukemic twin contained particle-related sequences that could not be detected in the leukocytes of his identical healthy sibling. These findings are inconsistent with hypotheses that postulate chromosomal transmission in the germ line of complete copies of the information required to produce malignancy and the associated virus particles.

329. MOLECULAR PROBING FOR A VIRAL ETIOLOGY OF HUMAN CANCER.

Spiegelman S, Schlom J, Axel R, Hehlmann R, Kufe D
Inst. Cancer Res., New York, N. Y.
Collect Pap Annu Symp Fundam Cancer Res; 25:547-573 1974

A so-called simultaneous detection test for reverse transcriptase and high molecular weight RNA (60-70S) was used to obtain evidence for the presence of RNA tumor viruses in biological materials from human sources. Procedures were worked out with the aid of materials containing B- and C-type viruses of avian, rodent, feline, or primate origin. They involved isolation of the hypothetical virions by high-speed centrifugation, disruption of the virions by ND-40 detergent and 0.1 M dithiothreitol, carrying out of a standard reverse transcriptase reaction, gradient analysis of the product, and examination of the 70S region of the gradient for the presence of tritiated DNA, which results from complexing of small DNA pieces to relatively large RNA molecules. This provided evidence for the presence of a reverse transcriptase using a 70S RNA template. Finally, tests were made for possible homologies between RNAs isolated from different human cancers and RNAs from known tumor viruses of non-human species. An example of such a test was the annealing of tritiated DNA, prepared with the aid of mouse mammary tumor virus RNA and reverse transcriptase, with the hypothetical human tumor virus RNA, prepared from human malignant breast tumor. The results showed that human breast cancer contains RNA homologous only to that of the murine tumor virus, that human leukemias, sarcomas, and lymphomas all contain RNA homologous to that of the murine Rauscher leukemia virus and not to that of mouse mammary tumor virus RNA, and that none of the human tumors contain RNA detectably related to the RNA of the avian myeloblastosis virus. It was pointed out that the mere existence of mouse mammary tumor virus-related RNA in human breast cancer and of Rauscher leukemia virus-related RNA in human leukemia, sarcoma, and lymphoma does not establish a viral etiology for these diseases.

B. MuMTV and Human Cancer: Enzyme and Protein Studies

330. MURINE TUMOR VIRUS-LIKE PROTEINS IN HUMAN BREAST CANCERS (MEETING ABSTRACT).

Black MM, Zachrau RE, Dion A, Shore B
Ny Med Col, New York, NY 10029, and Inst for Med Res, Camden, NJ 08103
Fed Proc; 35(3):570 1976

Previous studies disclosed antigenic similarities between some component(s) of immunogenic breast cancer tissues and some component(s) of murine mammary tumor virus (MuMTV) (Black et al, Cancer 35:121-128 1975). We now report on breast cancer tissue proteins whose physicochemical properties resemble MuMTV proteins; viz p55, p40 and p34. Sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) studies of 44 breast cancer tissue eluates demonstrated a prominent 50,000 MWt component (p50) in 30 (68%), a 34,000 MWt component (34) in 28 (64%) and a 40,000 MWt component (p40) in 26 (59%). All 3 components were found in 12 (26%) while all 3 were minimal or absent in 4 (9%). None of these components was prominent in eluates of normotypic breast tissues from 5 control and 9 cancerous breasts. In 8.5% PAGE, the p50 breast cancer proteins migrated similarly to p55 of MuMTV in 21 of 30 (70%) cases. Such cases were characterized by a higher proportion of prognostically favorable stages and MuMTV-like antigenicity than cases lacking this characteristic. (Author Abstract)

331. PURIFICATION AND CHARACTERIZATION OF THE DNA POLYMERASE OF HUMAN BREAST CANCER PARTICLES.

Ohno T, Sweet RW, Hu R, Dejak D, Spiegelman S
Institute of Cancer Research, College of Physicians and Surgeons of Columbia University, 701 West 168 Street, New York, N.Y. 10032
Proc Natl Acad Sci USA; 74(2):764-768 1977

Previous studies have identified human breast tumor particles possessing many of the features characteristic of RNA tumor viruses. In addition to the expected size (600S) and density (1.16 g/ml) these include possession of an outer membrane and an inner one surrounding a "core" containing a DNA polymerase and a large-molecular-weight (70S) RNA possessing detectable homology to the RNAs of the mouse mammary tumor virus (MMTV) and of the Mason-Pfizer monkey virus (MPMV). We report here the purification and characterization of the DNA polymerase from the human breast cancer particles. Its key properties are very similar to those of the RNA-dependent DNA nucleotidyltransferase (reverse transcriptases) found in MMTV and MPMV. Thus, like these viral enzymes, the purified human breast cancer DNA polymerase exhibits the following three features that together distinguish the known viral reverse transcriptases from normal cellular DNA polymerases: (i) a strong preference for oligo(dT) poly(rA) over oligo(dT) poly(dA) as a template for the synthesis of poly(dT); (ii) the acceptance of the highly specific oligo(dG) poly(rCm) as a template for the formation of poly(dG); (iii) the ability to use a viral RNA (AMV) as a template to fashion a faithful DNA

complementary copy; and (iv) its preference for Mg**++ over Mn**++. In summary, the data described here on the enzyme of the human breast cancer particles add further evidence of similarities to the viral agents associated with the corresponding malignancies in the mouse and monkey models. To date, an enzyme with these properties has not been detected in normal breast tissues or in benign tumors of the breast. (Author Abstract)

332. PARTICLES WITH RNA OF HIGH MOLECULAR WEIGHT AND RNA-DIRECTED DNA POLYMERASE IN HUMAN BRAIN TUMORS (MEETING ABSTRACT).

Cuatico W, Cho JR, Spiegelman S
Coll. Physicians Surgeons, Columbia U., New York, N.Y.
Proc Natl Acad Sci USA; 70(10):2789-2793 1973

The simultaneous detection test was used to study the etiology of human brain tumors. Fifty-one human brain tumors and 13 samples of histologically normal human brain tissue were analyzed. The tumors were found to contain 70S RNA and RNA-directed DNA polymerase encapsulated in a particulate component with a density of 1.17 g/ml; these particles could not be detected in any of the nonneoplastic tissues. The (3H)DNA synthesized by the brain tumor particles showed no detectable homology to the RNAs of avian myeloblastosis virus, Rous sarcoma virus, Rauscher leukemia virus, mouse mammary tumor virus, or visna virus; the particles did, however, satisfy the criteria which characterize RNA tumor viruses of animals. In some cases, enough tumor particles were present to permit hybridization tests; in such cases, homology was observed with the polysome RNA fraction from the same or similar tumor. The highest incidence of tumor particles were found in the following highly malignant tumors: glioblastoma multiforme, medulloblastoma, optic glioma, and oligodendroglioma. The particles were much less common in the following less malignant tumors: ependymoma, meningioma, and schwannoma.

333. PARTICLES CONTAINING RNA-INSTRUCTED DNA POLYMERASE AND VIRUS-RELATED RNA IN HUMAN BREAST CANCERS (MEETING ABSTRACT).

Axel R, Gulati SC, Spiegelman S
Coll. Phys. Surg., Columbia U., New York, N.Y.
Proc Natl Acad Sci USA; 69(11):3133-3137 1972

Tissues from 38 human breast adenocarcinomas were subjected to repeated centrifugation and added to a standard endogenous RNA-directed DNA polymerase reaction mixture. The mixtures were assayed for ability to synthesize a 70S RNA-DNA complex. Seventy-nine percent of adenocarcinoma tissues produced the 70S component, encapsulated with RNA-instructed DNA polymerase in a particle with the density characteristics of RNA tumor viruses. The complex was not detected in normal breast tissue or in fibroadenoma tissue. The DNA synthesized by the human RNA enzyme complex hybridized specifically with the RNA of mouse mammary tumor virus.

C. MuMTV and Human Cancer: Immunological Studies

334. MUMTV-LIKE CHARACTERISTICS OF HUMAN BREAST CARCINOMA IMMUNOGENS.

Black MM, Zachrau RE, Shore B
Dept. Pathology, New York Medical Coll., Fifth Ave. at 106th St., New York, NY 10029
Bibl Haematol; (43):559-564 1975

Studies of murine mammary tumor virus (MuMTV)-like antigenicity of human breast cancer tissues in relation to clinicopathologic characteristics and the presence of MuMTV-like proteins are summarized. When the WBC of a breast cancer patient were tested against diluted RIII milk samples at intervals ranging from less than mo to 39 mo after ribosomal precursor RNA and 18S and 28S ribosomal RNA, RNA positive responses were found in approx 30% of the patients. WBC responsive to RIII milk were cross-reactive to isolated MuMTV and gp55 from MuMTV. L-RE-positive autologous breast cancer tissues were preferentially responded to by RIII-positive WBC, both in vivo (89% positive response in the skin window test) and in vitro. Autologous-positive/RIII-negative WBC did not differentiate between L-RE-positive and L-RE-negative targets, but autologous-positive/RIII- positive WBC clearly showed more response to L-RE-negative targets (72%). Analysis of eluates of cryostat sections of benign and malignant breast lesions showed the following: (a) eluates of 39/46 breast cancer tissues contained a 50-55,000 molecular wt protein component (p50); (b) a B fraction was found in both malignant and benign tissue whose relative migration was 0.55 that of serum albumin and can serve as a reference point; (3) purified MuMTV gp55 is separable into three subfractions whose migrations are 0.80, 0.75, and 0.70; and (d) p50-containing eluates migrate to portions corresponding to one or more of the viral subfractions. Observance of the relative frequency of different p50 indicates that the presence of a p50-0.70 protein is preferentially associated with prognostically unfavorable cases. It is suggested that cross-reactivity between immunogenic breast cancer tissues and MuMTV is related to the presence, in the former, of a protein having physicochemical similarity to a particular subfraction of viral gp55. (29 refs)

335. PROGNOSTICALLY FAVORABLE IMMUNOGENS OF HUMAN BREAST CANCER TISSUE: ANTIGENIC SIMILARITY TO MURINE MAMMARY TUMOR VIRUS.

Black MM, Zachrau RE, Shore B, Moore DH, Leis HP
New York Med. Coll., N.Y.
Cancer; 35(1):121-128 1975

Independently derived data regarding lymphoreticuloendothelial (L-RE) responses, skin window tests, and WBC migration were used to examine the relationship between in vivo immunogenicity and in vitro antigenicity. A WBC migration procedure had been used to test cellular hypersensitivity of breast cancer patients' WBC to autologous and homologous breast cancer tissues and to murine milk containing murine mammary tumor virus (MuMTV). The response to autologous breast cancer tissues varied with the cancer tissue and the stage of the disease at mastectomy. Immunogens appeared in the in situ phase of the disease, provoked prognostically favorable L-RE responses, and possessed antigenic similarity to some components of MuMTV. The data suggest that the progression of human cancer is accompanied or preceded by a loss of tissue immunogenicity and/or diminished specific cellular hypersensitivity.

336. HORMONAL STIMULATION OF A VIRUS-RELATED ANTIGEN IN A HUMAN BREAST CARCINOMA CELL LINE, MCF-7.

Soule HD, McGrath CM, Long A, Rich MA
Department of Biology, MIchigan Cancer Foundation, Detroit, MI 48201
Proc Am Assoc Cancer Res; 17:167 1976

Sublines of MCF-7, a human breast carcinoma ceil line (JNCI, 51:1409, 1973) are inducible for an RNA tumor virus-like particle, 734B, (Nature, 252:247, 1974). Since MCF-7 cells contain cytoplasmic, steroid hormone receptors (J Biol Chem; 248: 6251, 1973) it was of interest to determine the influence of hormones on viral synthesis. 734B, the candidate human breast cancer virus, contains antigens which are cross-reactive with mouse mammary tumor virus (MuMTV) so that antisera containing multiple specificities reactive against MuMTV

antigens could be used to detect synthesis of viral antigen using immunofluorescence tests. The addition of progesterone stimulated a 20-fold increase in the synthesis of the cross-reactive antigens(s) in MCF-7 cells. The stimulation was dose-responsive and was maximal when progesterone was added to dividing cells. Other steroid hormones had no stimulatory effect. The antigens were detected in progesterone treated MCF-7 and MuMTV positive C3H tumor cells but not in human non-breast cell lines, nor in normal cells of murine and human origin. MCF-7 cells do not react with antisera against simian and murine type C particles. These results suggest that MuMTV information exists in malignant human breast tumor cells and the expression of the information is stimulated by progesterone. (Author Abstract)

337. HUMAN ANTIBODIES BINDING TO THE MOUSE MAMMARY TUMOR VIRUS: A NONSPECIFIC REACTION?.

Newgard KW, Cardiff RD, Blair PB
Dept of Pathol, School of Med, U of Calif, Davis, CA 95616
Cancer Res; 36(2):765-768 1976

Specific rabbit antisera and over 100 human sera were found to precipitate iodinated mouse mammary tumor virus (MTV). The specificity of these reactions was tested in competitive inhibition studies. Three classes of reaction could be distinguished. The Class 1 reaction was the most specific; it could be inhibited only by MTV and was observed exclusively with rabbit anti-MTV. The Class 2 reaction was apparently against mouse cell determinants; it could be inhibited not only by MTV but also by mouse lactating mammary gland and was characteristic of rabbit anti-mouse lactating mammary gland. The Class 3 reaction was the least specific; it could be inhibited not only by MTV and mouse lactating mammary gland but also by dog milk. All of the human sera tested exhibited Class 3 reactivities.

338. IMPLICATIONS OF HUMORAL ANTIBODY IN MICE AND HUMANS TO BREAST TUMOR AND MOUSE MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGENS.

Bowen JM, Dmochowski L, Miller MF, Priori ES, Seman G, Dodson ML, Maruyama K
Department of Virology, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Houston, TX 77025
Cancer Res; 36(2):759-764 1976

As a part of a program directed toward the elucidation of the role of viruses in mouse and human breast cancer, a variety of immunological techniques were applied to a study of the humoral immune response of mice and of humans to their breast tumors. Tumor-bearing mice were found to produce antibodies against a complex array of tumor cell-associated antigens, including mouse mammary tumor virus (MMTV) components, heterophile and Forssman-like antigens, embryonic antigens, and possibly other tumor-associated antigens. Mice bearing MMTV-positive tumors had high titer antibodies against both viral and heterophile antigens. Tumor-free mice, whether of high or low mammary cancer strains, were remarkably free of antibodies that could label MMTV particles, although some sera contained antibodies to viral components. Patients with breast cancer also had antibodies against a variety of antigens associated with their own and homologous breast cancer cells. These antibodies reacted with heterophile, embryonic, and other tumor-associated antigens, some of which appeared to be viral. Sera of some patients with breast cancer gave positive immunofluorescence reactions with mouse mammary tumor cells grown in tissue culture and producing MMTV. Most of these reactions were due to heterophile antibodies in the sera, but a small number of sera contained antibodies apparently directed specifically toward MMTV particles, as determined by immunoperoxidase electron microscopy. Although human-mouse cross-reactions must be interpreted with caution, these data suggest that a virus putatively associated with human breast cancer is antigenically related to MMTV.

339. ANTIVIRAL AND ANTITUMOR ANTIBODIES IN MOUSE AND HUMAN BREAST CANCER (MEETING ABSTRACT).

Bowen JM, Dmochowski L, Seman G, Scanlon M
Dept of Virology, The University of Texas System Cancer Center M D Anderson Hospital and Tumor Institute, Houston, Texas 77025
Proc Am Assoc Cancer Res; 17():53 1976

The distribution of antibodies to antigens of mouse mammary tumors (MMT) in sera of mice and of breast cancer patients was studied by immunofluorescence (FIF) with both fluorescein- and peroxidase-conjugated reagents. Both young and adult mice of both sexes of several high-(A/Dm;A/Tex;RIII/Dm;C3H/Bi/Dm;C3H/He/Tex) and low-(C57Bl/6/Tex;BALB/c/Tex;CBA/Tex;DBA/2/Tex; NZB/Cr;Nzw/Cr;SJL/J/Cr) MMT strains, including tumor-bearing females, were studied. All sera were tested against cells of a mouse mammary tumor virus (MMTV)-producing C3H/He/J/Tex MMT line. Sera of most tumor-bearing and adult tumor-free females and of some adult males of high-MMT strains were positive by FIF. The reaction was removed only by absorption of sera with MMTV or MMT preparations. Sera of young high-MMT mice of both sexes were negative. Sera of low-MMT strain mice, when positive, became negative after absorption with heterophile antigens. Sera of some (20%) breast cancer patients, found positive with MMT cells, became negative following absorption with MMTV or MMT preparations, but not with heterophile antigens. Results indicate the presence of MMTV and tumor-specific antibodies in sera of mice and of humans which appear to be against an antigen shared by MMTV. (Author Abstract)

340. ANTIBODY REACTING WITH MOUSE MAMMARY TUMOR VIRUS IN SERUM OF BREAST CARCINOMA PATIENTS.

Holder WD, Peer GW, Bolognesi DP, Wells SA
Dept. Surgery, Duke Univ. Medical Center, Durham, NC
Surg Forum; 27:102-104 1976

Immunoelectron microscopy (IEM) studies were performed to determine if the presence of antibody against mouse mammary tumor virus (MMTV) is helpful in the preoperative detection of breast lesions. Sera from 20 patients with suspected breast carcinoma were obtained prior to surgery. Normal sera were obtained from 18 patients with a clinically benign status. An indirect immunoferritin method was used with viable C3H/HeJ mouse breast tumor cells as a source of MMTV. Labeling of both budding MMTV and the C3H/HeJ cell surface was found in serum samples from all 20 patients with breast cancer. Only C3H/HeJ cell surface labeling was noted in the sera from 14 of the 18 control women; however, in 2 of these patients, the sera labeled budding MMTV. These women are known to have worked with laboratory mice and cultures containing MMTV. This method may be used for serologically testing for this malignant lesion. (2 refs)

341. LYMPHOCYTE TRANSFORMATION IN VITRO TO RIII MOUSE MILK ANTIGEN AMONG WOMEN WITH BREAST DISEASE.

Cunningham-Rundles S, Feller WF, Cunningham-Rundles C, Dupont B, Wanebo H, O'Reilly R, Good RA
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021
Cell Immunol; 25(2):322-327 1976

The cell-mediated immune responses of 110 women with benign or malignant breast disease, 20 women with endometrial, ovarian, or cervical cancer, and 52 normal women not taking oral contraceptives or other medication were tested in an in vitro lymphocyte transformation assay with an antigen preparation made from RIII mouse milk containing mammary tumor virus. Fifty percent of the patients with breast disease responded positively to the milk preparation. Twenty-five percent of normal women or women with other gynecological malignancies also responded positively to the antigen. Examination of the histological patterns observed among patients with malignant or benign breast disease revealed no apparent differences between responders and nonresponders. These results demonstrate a similar response pattern among women with malignant or benign breast disease. In addition, a subpopulation of normal women with positive response to this antigen is clearly defined. This response may reflect the expression of an early stage of antigen formation, the future course of which might be determined by the interaction of environmental and genetic factors. It is also possible that either the expression of the antigen or response to it may be under genetic control. Although the practical use of the RIII mouse milk preparation is indicated by this report, the molecular nature of the antigen and its implied relationship to a putative human virus remains to be clarified. (18 refs)

342. IMMUNOLOGICAL RELATIONSHIPS BETWEEN MUMTV, 734B AND A VIRUS-LIKE PARTICLE ISOLATED FROM HUMAN MILK.

Mcgrath CM, Furmanski P, Soule H, Grant P, Longley C, Rich MA
Division of Biological Sci., Michigan Cancer Foundation, Detroit, Mi 48201
Proc Am Assoc Cancer Res; 16:164 1975

734B, the candidate human breast cancer virus was isolated from cultures of human breast cancer cells (Nature 252:247, 1974). Cells synthesizing 734B specifically react with anti-MuMTV sera, measured in immuno-fluorescence tests. Absorption experiments suggest that the cross-reactive cell-associated antigen is a structural protein of 734B. Isotopically labelled proteins from purified 734B particles bind specifically to anti-MuMTV immunoadsorbant columns. One protein of 734B specifically eluted from these affinity columns co-electrophoreses with an MuMTV structural protein. The major MuMTV protein (gp52) is absent in 734B. Sub-virus cores prepared from some human milks also contain a protein which co-electrophoreses with an MuMTV structural protein. This protein from human milk cores also binds to the anti-MuMTV immunoadsorbant columns. These experiments suggest that a relationship exists between 734B, the endogenous human milk virus-like particle, and MuMTV, the etiologic agent for breast cancer in mice. (Author Abstract)

343. EFFECT OF MURINE MILK SAMPLES AND HUMAN BREAST TISSUE ON HUMAN LEUKOCYTE MIGRATION INDICES.

Black MM, Moore DH, Shore B, Zachrau RE, Leis HP
New York Med. Coll., N. Y.
Cancer Res; 34(5):1054-1060 1974

Leukocytes from adult women with and without benign and malignant breast lesions were tested against cryostat sections of autologous and homologous benign and malignant (in situ and invasive) breast lesions. Simultaneous tests were made against RIII mouse milk samples that contain murine mammary tumor virus and against virus-free mouse milk samples from RIIIf and C57BL mice. Observations were also made on the response to a common environmental antigen (Varidase). The migration of leukocytes from breast cancer patients was commonly inhibited by Varidase but was not inhibited by virus-free mouse milk samples or by benign breast tissues. However, migration inhibition (greater than 25%) was found in 31% of breast cancer patients tested against RIII milk, in 33% of tests against homologous in situ breast cancer, in 29% of tests against autologous invasive breast cancer, and in 16% of tests against homologous invasive breast cancer tissues. Responsiveness to breast cancer tissues was correlated with a high degree of cross-reactivity against RIII mouse milk. Conversely, leukocytes that responded to RIII milk cross-reacted in most of the tests against homologous in situ breast cancer and in approximately one-third of the tests against invasive breast cancer but were nonresponsive to RIIIf milk, C57BL milk, and benign breast lesions. It appears that the antigenicity of human breast cancer tissue is largely a reflection of a component that is similar to that found in murine mammary tumor virus-infected lactating mammary parenchyma.

344. A FAMILY STUDY OF REACTIVITY TO VIRAL AND MAMMARY TUMOR ASSOCIATED ANTIGENS.

Wiseman C, Bowen J, Blumenschein G, Hersh E, Jackson B, Sullivan M
Univ. of Texas System Cancer Center M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77025
Proc Am Assoc Cancer Res; 17:191 1976

A breast cancer patient and her family were studied for immune reactivity to antigens of human and mouse breast cancers. Methods included fixed immunofluorescence (FIF), membrane immunofluorescence (MF), humoral cytotoxicity, lymphocyte blastogenesis and migration inhibition (MI). Monolayers were prepared from 2 human breast cancer lines, MCF/7 and MDA-MB 231, and from MMT-1 derived from a mouse mammary tumor. The propositus case, AC, was aged 43, and had a radical mastectomy and radiation for intraductal breast cancer 9 months prior to study. Family history of cancer was strong. Positive FIF to both human lines was seen in sera of the propositus and 7 of 8 relatives, even after absorption of heterophile, normal breast and mouse antigens. MF and vigorous cytotoxicity to MCF/7 was shown by AC but only 2 others were positive. Studies with MMT-1 showed FIF positive in 6 of 8, including AC. MF against MMT-1 was positive in 5 of 8 but absent in A.C. Sonicated mouse mammary tumor virus (MMTV) produced MI in all 6 individuals tested. Lymphocyte blastogenesis studies demonstrated impaired lectin responses in AC. Lectin responses were normal in 6 of 7 relatives. MMTV stimulated 3. Reactivity to the above tests occurs in less than 20% of normals. The results suggest a familial association of these immune responses. (Author Abstract)

345. LYMPHOCYTE INHIBITION BY MAMMARY TUMOR VIRUS IN PATIENTS WITH BREAST CANCER.

Moulton A, Lo Gerfo P, Suciu-Foca N, Silverstein G
Coll. Physicians Surgeons, Columbia U., New York, N. Y.
J Surg Res; 16(6):592598 1974

Peripheral blood lymphocytes from women with active breast cancer, benign breast disease, and nonrecurrent breast disease after mastectomy were tested for their ability to respond to the antigens of mouse mammary tumor virus (MTV) in normal and autologous serum using the mixed lymphocyte culture (MLC) and phytohemagglutinin (PHA) stimulation tests. The incidence of individuals responding to

the virus by lymphocyte blastogenesis was significantly lower in the group with active breast cancer; this impairment of reactivity was proportional to the extent of the disease. This type of correlation was seen when the lymphocytes were grown with both normal and autologous serum, although the degree of stage dependency was less marked with lymphocytes grown in autologous serum. Autologous serum strongly decreased the incidence of responders among the nonrecurrence group. A significant reduction of MLC activation was seen in the presence of autologous serum as compared with pooled normal serum in the cancer patients. Sera from the active cancer patients only decreased the PHA responsiveness of autologous lymphocytes below the levels seen in normal serum. Serum alpha globulins were elevated in the patients with active disease; there was no correlation between the levels of alpha globulin and the degree of lymphocyte inhibition. The extent of tumor growth correlated positively with serum tumor-associated antigen, cytotoxic antibodies, and serum blocking factors.

346. IMMUNOLOGIC STUDY OF AN ONCORNAVIRUS ISOLATED FROM A HUMAN CANCER CELL LINE.

Ilyin KV, Irlin IS, Bykovsky AF, Spure ZZ, Miller GG, Abenova UA, Zhdanov VM
N. F. Gamaleya Inst. Epidemiol., USSR Acad. Med. Sci., Moscow
Cancer; 34(3):532-538 1974

An oncornavirus of type B isolated from HEp2 cells was compared immunologically with other type B viruses isolated from human, monkey, and mouse tissues. Immune serum was prepared by inoculation of rabbits with HEp2 virus antigen treated with ether; the surface antigens of the virus were destroyed and the rabbits were immunized with the group-specific (internal) antigen. Tests with intracellular and extracellular HEp2 virus antigens revealed identical precipitation lines in immunodiffusion tests. The same results were obtained in comparative tests with HEp2 viral antigens and other type B viruses isolated from continuous human cell lines; no cross reaction was seen with the H22 type C virus. No cross reaction was seen between the HEp2 virus and the mouse mammary tumor virus, while rhesus monkey type B oncornavirus gave the identical precipitation line with the HEp2 test system. No detectable antigens were found in bovine serum. The test system studied apparently revealed a group-specific antigen common or related to the Mason-Pfizer group-specific antigen.

347. AN ANTIGEN IN HUMAN BREAST CANCER SERA RELATED TO THE MURINE MAMMARY TUMOUR VIRUS.

Muller M, Grossmann H
Inst. Path., Dresden, East Germany
Nature New Biol; 237:116-117 1972

Thirty-six sera from women with mammary carcinoma were reacted in micro-double-diffusion tests with three highly specific rabbit hyperimmune sera against the mammary tumor virus (MTV). Ten of 36 sera reacted with each of the three anti-MTV sera, whereas 35 sera from donors without mammary carcinoma failed to react with the anti-MTV sera. The factor detected in ten human breast cancer sera appeared to share common antigenicity with a constituent of the outer MTV-particle coat.

348. NEUTRALIZATION OF MURINE MAMMARY TUMOR VIRUS BY SERA OF WOMEN WITH BREAST CANCER.

Charney J, Moore DH
Inst. Med. Res., Camden, N. J.
Nature (Lond); 229(5287):627-628 1971

Neutralization tests were carried out to determine whether murine mammary tumor virus (MTV) could be neutralized by serum prepared from breast cancer patients. In experiments with human serum, sera were used practically undiluted, and MTV was used in concentration of about 100 ID50/0.1 ml. Inoculation of MTV treated with human breast cancer sera resulted in a mean incidence of MTV infection in C57BL mice of 69% compared to an 87% incidence of infection in mice inoculated with MTV treated with a control serum prepared from normal human subjects. The presence of neutralizing antibodies in sera from human breast cancer patients and their absence from normal human sera indicated a viral etiology for the human disease.

349. SPECIFICITY OF HUMAN ANTIBODIES TO INTRACYTOPLASMIC TYPE-A PARTICLES OF THE MURINE MAMMARY TUMOR VIRUS.

Muller M, Zotter S, Kemmer C
Medical Acad., Carl Gustav Carus," Schuberstrasses 15, 8053 Dresden, German Democratic Republic
J Natl Cancer Inst; 56(2):295-303 1976

The specificity of the human antibody reaction to intracytoplasmic inclusions of mouse mammary tumors rich in intracytoplasmic type-A particles (iAp) was investigated. Large-scale studies showed that antibodies previously detectable in women with proliferating mastopathy or breast cancer were directed to iAp of mouse mammary tumor virus. Immunofluorescence revealed the human antibodies to be bound only by those tumors producing a certain amount of iAp clusters visible by light microscopy. The intensity of the reaction corresponded to the iAp content of every tumor tested as revealed by electron microscopy and rabbit antisera to iAp. The fluorescence patterns obtained with positive human sera were similar to those obtained with rabbit antisera specific for iAP and resembled the tissue distribution patterns of iAp inclusions strained by acid fuchsin. The reaction with human sera was entirely blocked by rabbit antisera to iAp and, less so, by rabbit or mouse antisera to B particles. The human antibody activity was exhaustively absorbed by purified iAp or purified and disrupted B particles, indicating that the human antibodies were directed to antigenic components shared by iAp and B particles. Preliminary immunoperoxidase studies supported the assumption that the human antibodies were bound to the iAp membrane; technical details might have accounted for the finding that the human antibodies reacted with the iAp but not with B particles in situ.

350. CROSSED REACTION OF HUMAN BREAST CANCER AND FIBROCYSTIC MASTOPATHY WITH MURINE MAMMARY CARCINOMAS: LOCATION OF THE ANTIGEN IN A-PARTICLES OF MAMMARY TUMOR VIRUS.

Mueller M, Kemmer C, Zotter S, Grossmann H, Michael B
Carl Gustav Carus Med. Acad., Dresden, Germany
Arch Geschwulstforsch; 41(4):100-106 1973

The indirect immunoferritin technique was used to determine whether antibodies found in women with breast cancer and fibrocystic mastopathy react with intracellular clusters of A-particles which are immature precursors of the B-particles of mouse mammary tumor virus. Mouse tumor MT4814, obtained by passage in syngeneic CBA/Bln mice was fixed in neutral 4% formalin by shaking for 10 min. Cells obtained in this way were washed three times in phosphate-buffered physiological saline and incubated for 3 hr at room temperature with 0.1 ml of C89 serum from a patient with fibrocystic mastopathy, blood donor serum, or phosphate-buffered physiological saline. After washing three times with physiological saline, cells were incubated for 2 hr at room temperature with 0.1 ml ferritin-serum. Examination under the electron microscope showed that ferritin granules were deposited only in tumor cells incubated with C89 serum. These granules were present in clusters of A-particles or surrounded

individual A-particles or groups of them. Ferritin deposits on the cytoplasmic membrane are also considered specific since they were not present in controls. No ferritin deposits occurred on B-particles. These results, which agree with those obtained with immunofluorescence techniques, provide evidence for the existence of a human breast cancer virus which is immunologically related to mouse mammary tumor virus.

351. ONCORNAVIRUS MARKERS ON PERIPHERAL LYMPHOCYTES OF BREAST CANCER PATIENTS. (MEETING ABSTRACT).

Wiseman C, Robinson B, Bowen J, Blumenschein G
M. D. Anderson Hosp and Tumor Inst, Houston, TX 77030
Proc Am Assoc Cancer Res; 18:172 1977

Oncornavirus antigens can be detected in normal tissues in animals in several viral-associated malignancies. Although viral associated antigens have been reported in various human cancers by many different techniques, we report here data suggesting their presence also in non-malignant tissue of breast cancer patients. Viable peripheral blood lymphocytes (PBLs) from buffy-coat or Ficoll-Hypaque concentrates were tested with several antisera by indirect immunofluorescence. Antiserum A was generated by immunizing a rabbit with purified glycoproteins of mouse mammary tumor virus (M-MTV). In positive cases, typical membrane immunofluorescence could often be identified in 50% or more of the PBLs examined. Of 20 breast cancer patients, reactive cells were identified in 14, while only 2 of 10 normal age-matched women had reactive PBLs. The patient group was significantly more reactive, $p = 0.013$, Fischer exact test. Absorption of A with MMTV extinguished reactivity. Goat anti-GP52, from Dr Wade Parks, produced results similar to those with A. Goat anti-Rauscher serum or normal rabbit serum reacted in only 2 of 18 and 0 of 19 tests respectively. While the nature of these reactions needs further definition, these findings are consistent with human exposure to putative tumor-associated virus. (Author Abstract)

352. LEUKOCYTE MIGRATION INHIBITION IN HUMAN BREAST CANCER WITH MOUSE MAMMARY TUMOR VIRUS, GP-52 AND GP-70. (MEETING ABSTRACT).

McCoy J, Dean JH, Herberman RB
NCI, Bethesda, MD 20014
Proc Am Assoc Cancer Res; 18:177 1977

Direct migration inhibition (LMI) assays were conducted with leukocytes from breast carcinoma, benign breast disease, other cancer patients, and normal donors using mouse mammary tumor virus (MMTV), its major glycoprotein (gp52) and murine leukemia virus (MuLV) glycoprotein (gp70) as antigens. 13/15 (83%) breast carcinoma and 3/5 benign breast disease patients reacted with MMTV, while 1/16 (6%) normal donors and 0/9 patients with other cancers reacted. LMI with gp52 was positive in 39/60 (65%) breast carcinoma, 8/15 (53%) fibrocystic and 2/11 (18%) fibroadenoma patients, 1/15 (7%) normal donors and 3/15 (20%) patients with other cancers. Specificity studies with gp70 preparations of Rauscher leukemia and Kirsten sarcoma virus gave approximately 40% incidence of reactivity of breast carcinoma patients, 20% with benign breast disease, 10% normal donor and 0% with patients with other cancers. Results suggest that many breast carcinoma and benign breast disease patients have LMI reactivity against glycoproteins of MMTV and MuLV. Due to lack of restriction of LMI specificity to antigens of MMTV in both patients with malignant and benign breast disease, caution must be presently taken in interpreting the etiologic significance of these findings. (Author Abstract)

353. ONCORNAVIRUS-LIKE PARTICLES IN HELA CELLS. II. IMMUNOLOGICAL CHARACTERIZATION OF THE VIRUS.

Bauer H, Daams JH, Watson KF, Molling K, Gelderblom H, Schafer W
Robert Koch-Inst., Berlin, West Germany
Int J Cancer; 13(2):254-261 1974

The immunological characteristics of an oncornavirus-like agent which has been isolated from HeLa cells of human origin were studied by immunodiffusion and gel electrophoresis. The pattern of the major protein constituents of the HeLa virus was similar to that of known oncornaviruses (avian myeloblastosis virus and murine leukemia virus (MuLV). Six polypeptides with molecular weights (mw) between 12,000 and 28,000 daltons and two glycopolypeptides with mw of about 60,000 to 80,000 daltons were detected by SDS-polyacrylamide gel electrophoresis. No serological cross-reaction was found between the HeLa virus and B-(mammary tumor virus and avian oncornaviruses) and C-type (MuLV and feline leukemia virus oncornaviruses). Essentially, none of two inter-species-specific antigen determinants described in mammalian C-type viruses was detected in the HeLa virus. However, a distinct serological relationship was found between the HeLa virus and the Mason-Pfizer monkey virus in that these viruses share at least two antigens in the mw range of 16,000 and 28,000 daltons, respectively. Thus, the HeLa virus appears to be oncornavirus-like but structurally distinguishable from the classical B-type and C-type particles. These results provide further evidence for the existence of a new group of oncornavirus-like particles.

354. SPECIFICITY OF CELL-MEDIATED IMMUNITY IN MOUSE-HUMAN CROSS-REACTIONS: FORMAL DISCUSSION.

Parks W
Natl. Cancer Inst., Bethesda, MD 20014
Cancer Res; 36(2):559-869 1976

Viruses and immune responses to mouse breast cancer viral antigens are discussed. A substance, with a molecular weight of 52,000, which is related to the mouse mammary tumor virus glycoprotein has been reported to react with the lymphocytes of breast cancer patients. Other investigators concluded that there were several classes of binding reactions, and that the only types they observed with human sera were nonspecific. The need to adhere to criteria of specificity is emphasized. The best measures of specificity for an observed reaction in its relationship to viruses are those that involve purified viral polypeptides.

355. BIOLOGICAL CONSIDERATIONS OF TUMOR-SPECIFIC AND VIRUS ASSOCIATED ANTIGENS OF HUMAN BREAST CANCERS.

Black MM, Zachrau RE, Shore B, Leis HP
New York Medical Coll., Flower and Fifth Ave. Hosps., New York, NY 10029
Cancer Res; 36(2):769-774 1976

The nonrandom development of human breast carcinomas, the characteristics of preinvasive breast cancers, and the heterogeneous behavior of invasive breast carcinomas, especially with regard to tumor-host interactions, were considered to support the individuality of patients and their lesions. This is in contrast to the practice of referring to breast cancer as if it were a homogeneous, single entity. In vivo and in vitro studies were reviewed; they revealed that in situ carcinomas precede invasive carcinomas. Microscopically demonstrable lymphoreticuloendothelial responses, skin window tests, and leukocyte migration tests all indicated that tumor-specific antigenicity develops in the early phases of mammary carcinogenesis. This antigenicity is expressed

maximally in in situ carcinomas without associated invasive breast cancer and minimally in invasive breast cancer with metastases. Immunogenic breast cancer tissues commonly contain a protein component with antigenic and physicochemical properties that are similar to those of a protein component of murine mammary tumor virus. It was concluded that immunological phenomena play a role in the behavior of breast cancer in individual patients. Immunoprophylaxis appears attainable, except in patients who have already had the invasive disease. The necessity of individualization of treatment, not only in immunotherapy but in chemotherapy and radiotherapy as well, was stressed.

356. STRUCTURAL, ANTIGENIC, AND BIOLOGICAL CHARACTERISTICS OF PRECANCEROUS MASTOPATHY.

Black MM
Department of Pathology, New York Medical College, New York, New York 10029
Cancer Res; 36(7):2596-2604 1976

A biologically significant relationship between precancerous mastopathy (PCM), in situ carcinoma (ISC), and invasive breast carcinoma is evidenced by the following: (a) PCM and ISC are commonly associated with each other and with invasive breast cancer; (b) Stage 0 PCM and ISC are both associated with an increased risk of subsequent breast cancer; (c) patients with Stage 0 PCM and ISC are more similar to invasive breast cancer patients than to patients with normotypic breast lesions in regard to family history of breast cancer and parity characteristics; (d) PCM and ISC resemble invasive breast cancers and differ from normotypic mammary epithelium in regard to epithelial cell-lymphoreticuloendothelial relationships; (e) PCM and, particularly, ISC are associated with distinctive immunogenic components; (f) prognostically significant immunogens of invasive breast cancer tissues are related to and antigenically similar to immunogenic components of associated ISC; (g) immunogenic cancers (ISC and invasive) from different patients are antigenically similar to one another; (h) immunogenic cancers (ISC and invasive) from different patients are antigenically similar to some component of murine mammary tumor virus. (Author Abstract)

357. FULMINATING BREAST CANCER (POUSSE EVOLUTIVE) IN TUNISIA: CLINICAL AND IMMUNOLOGIC FEATURES (MEETING ABSTRACT).

Mourali N, Tabbane F, Djaziri M, Cammoun M, Souissi T, Attia AB
Inst Salah Azaiz, bab Saadoun, Tunis, Tunisia
Third International Symposium On Detection And Prevention Of Cancer; 276-277 1976

In previous reports we have described a fulminating form of breast cancer in Tunisia which has been attributed by Denoix to a depression of immunologic control. At the Institute Salah Azaiz (ISA), we observed this form, which is called pousse evolutive (PEV) in 57% of our last 600 breast cancer patients. 70% of the 47 patients with breast cancer diagnosed in the course of pregnancy had PEV, suggesting a contribution of constant hormonal stimulation to this unusual manifestation. Response to standard treatment is poor, with less than 25% of PEV patients surviving three years. Between October 1974 and October 1975, a battery of immunologic tests have been utilized in the study of 88 consecutive breast cancer patients, including 59 (67%) with PEV, in order to search for immunologic differences between the PEV and non-PEV cases. Skin testing with DNCB, trichophyton, monilia and other common antigens did not reveal any differences between PEV and non-PEV patients, but there appeared to be less skin test reactivity against breast cancer associated antigens in the PEV cases. Immunoglobulin levels were markedly abnormal but other immunologic markers, including EBV titers and antibodies to mouse mammary tumor virus associated antigens, did not distinguish between PEV and non-PEV cases. (Author Abstract)

358. COMMON ANTIGENS IN ONCORNAVIRUSES FROM CONTINUOUS HUMAN CELL LINES AND MASON-PFIZER VIRUS.

Irlin IS, Ilyin KV, Bykovsky AF, Miller GG, Volkova MY, Lozinsky TF, Zhdanov VM
N. F. Gamaleya Inst. Epidemiol. Microbiol., Moscow, USSR
Intervirology; 2(2):95-99 1973

Extracellular antigens were prepared from extracellular viruses isolated from human HEp2, HeLa, DAPT, RH, Detroit 6, AO, and A1 cells. Immune sera against Mason-Pfizer monkey virus (MPMV) and HEp2 virus formed identical precipitation lines with antigens of HEp2, Detroit 6, and RH cells in immunodiffusion tests. In immunodiffusion reactions with autoradiography, MPMV serum reacted with RH cell antigen but not mouse mammary tumor virus (M-MTV) antigen, while MMTV serum reacted with MMTV antigen but not RH cell antigen. MPMV serum reacted with homologous viral antigens. Both MPMV and HEp2 sera reacted with cellular and extracellular antigens from HEp2, HeLa, DAPT, RH, Detroit 6, AO, and A1 cell cultures, as well as with MPMV antigens. Neither MMTV-related antigens nor gs3 antigen of the C-type viruses were revealed in these cultures. Thus, these 7 human cultures, all of which produce B-type oncornaviruses, contain both extracellular and intracellular antigen which is closely related to the antigen of MPMV.

359. AN ONCORNAVIRUS ISOLATED FROM HUMAN CANCER CELL LINE.

Ilyin KV, Bykovsky AF, Zhdanov VM
Acad. Med. Sci., Moscow, USSR
Cancer; 32(1):89-96 1973

Some morphological, biophysical, biochemical, and immunological properties of a virus isolated from a clone of continuous cell line that was derived from human cancer tissue (HEp-2 cells) were examined. The clone of HEp-2 cells retains human karyotype and has no heterogeneous contamination. Injection of the cells and the virus into mice of C3H/Sn, C3H/H2P, BALB/c lines and into newborn hamsters did not produce tumors in animals. Intracellular virus possesses morphological characteristics of oncornaviruses type A and B; extracellular virus has the properties of oncornaviruses type B. The virus bands at rho = 1.16 g/ml in sucrose density gradients, and the production of it is inhibited by actinomycin D. The virions contain reverse transcriptase, and the products of reaction are double-stranded DNA and RNA:DNA hybrids. The virus is immunologically distinct from mouse mammary tumor virus. These results lead to the conclusion that the virus isolated may be considered as an oncornavirus of human origin. Another explanation is that the virus was introduced into the culture with calf serum added to the cultural medium. However, the latter possibility is scarcely probable because the comparative study of several continuous human cell lines grown in the medium with calf serum showed that type C particles are associated only with leukemic cells, and type B particles were found in cancer cells.

360. B-TYPE ONCORNAVIRUSES ISOLATED FROM CONTINUOUS HUMAN CANCER CELL LINES.

Bykovsky AF, Miller GG, Yershov FI, Ilyin KV, Zhdanov VM
N. F. Gamaleya Inst. Epidemiology Microbiol., Moscow, USSR
Arch Gesamte Virusforsch; 42(1):21-35 1973

Eleven lines and sublines of larynx carcinoma (HEp-2), cervical cancer (HeLa) and dedifferentiated astrocytoma

(DAPT) cells were examined and viruses were isolated from eight lines. Electronmicroscopic, biophysical and biochemical examinations of the viruses showed that they belong to the B-type oncornaviruses. The virions had a size of 100 to 150 nm, they banded at densities of 1.16 to 1.17 g/ml/ in sucrose gradients and RNA from the virions contained 60-70S component. The reproduction of the viruses was inhibited by actinomycin D, and the virions possessed reverse transcriptase (RNA-dependent DNA polymerase) activity. The isolated viruses differed antigenically from mouse mammary tumor virus. The cell cultures preserved the human karyotype and were not contaminated with foreign cells. Since all tissue cultures were maintained in the presence of bovine serum, it may be supposed that the virus isolates could be contaminants of bovine or swine origin. This possibility is not excluded by these experiments, although oncornaviruses of the B type have not yet been discovered in cattle or swine.

361. HISTOLOGICAL STUDY OF IRON DEPOSITS IN MAMMARY GLANDS OF MICE.

Seman G, Bowen JM, Dmochowski L
Dept. of Virology, The Univ. of Texas System Cancer Center M.D. Anderson Hospital and Tumor Institute, Houston, Texas 77025
Proc Am Assoc Cancer Res; 17:110 1976

Iron metabolism, and more specifically protein-bound iron (lactotransferrin), appear to be of importance in human breast cancer. In an attempt to find an animal model system demonstrating a possible relationship between the presence of iron and hormonal, genetic or viral factors in mammary tumorigenesis, sections of mammary glands of mice of a number of strains have been stained with Mallory's method, which reveals ferric iron as Prussian blue. Mammary glands of pregnant lactating or nonlactating breeder mice of strains A/Jax; DBA2/Jax; RIII/Dm, C3H/HeJ/Dm, BALB/c/Tex, and C57/Bl/6/Tex, as well as mammary tumors of RIII/Dm and C3H/HeJ/Dm have been examined. Iron deposits were demonstrated in epithelium of resting mammary glands and in lymph nodes of breeder mice of all strains, but not of C57/Bl/6/Tex mice. Lactating glands of mice of all strains or tumors contained no iron detectable by Mallory's method. Iron is deposited in dense granules of epithelial cells as observed by electron microscopy. The apparent lack of iron in mammary glands of C57/Bl/6/Tex mice and the known resistance to MMTV may be genetically related. The results also suggest a close relationship between iron in mouse mammary tissue and hormonal status of the animals. (Author Abstract)

VIII. CULTIVATION AND CHARACTERIZATION OF MuMTV INFECTED CELL LINES

362. REPLICATION OF MOUSE MAMMARY TUMOR VIRUS IN TISSUE CULTURE. 1. ESTABLISHMENT OF A MOUSE MAMMARY TUMOR CELL LINE, VIRUS CHARACTERIZATION, AND QUANTITATION OF VIRUS PRODUCTION.

Sarkar NH, Pomenti AA, Dion AS
Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021
Virology; 77(1):12-30 1977

Certain aspects of mouse mammary tumor virus (MuMTV) morphology are discussed, along with the kinetics of virus production in the MuMT-73 cell line and the biochemical and immunological characteristics of the tissue-culture-grown virus. Thin-section electron microscopy of the cultured cells showed the presence of budding and extracellular, mature, B-type virions. These findings were confirmed by negative staining. Immunological testing showed that a certain percentage of the cells were always positive for MuMTV antigens but that all cells were negative for murine leukemia virus antigens. Polyacrylamide gel electrophoresis of the purified virus revealed five major polypeptides, two glycopeptides with molecular wts of 55,000 and 34,000 and three nonglycopeptides with molecular wts of 28,000, 18,000, and 12,000. Using immunofluorescence, it was discovered that between 0 and 3 days after seeding, 25% of the cells were weakly positive for MuMTV antigens. Max fluorescence was attained at about day 6 and maintained until day 10. During this period of max viral antigen synthesis, only about 35% of the cells were positive. Reverse transcriptase measurements demonstrated that the amount of virus that could be collected from the tissue culture depended upon the time of harvest. Max yield occurred 4-6 days after the cells became confluent. Hydrocortisone and dexamethasone stimulated MuMTV production. (58 Refs)

363. COMPARISON OF THE GROWTH PROPERTIES IN VITRO AND TRANSPLANTABILITY OF CONTINUOUS MOUSE MAMMARY TUMOR CELL LINES AND CLONAL DERIVATIVES.

Butel JS, Dudley JP, Medina D
Dept of Virology and Epidemiology and of Cell Biology, Baylor Coll of Medicine, Houston, TX 77030
Cancer Res; 37(6):1892-1900 1977

Five continuous mouse mammary tumor cell lines and 12 clonal derivatives have been established from tumors arising in BALB/c or C3H mice either spontaneously or in response to viral (mammary tumor virus), hormonal (17beta-estradiol), or chemical (7,12-dimethylbenz(alpha)anthracene) stimuli in vivo. The cell lines were examined for the following in vitro growth parameters: plating efficiency, saturation density, population-doubling times, colony formation on plastic surfaces, and anchorage-independent growth in methylcellulose. The majority of the mammary tumor cell lines were transplantable in syngeneic, immunocompetent mice and gave rise to tumors composed of epithelial cells. There was no growth parameter in vitro which invariably correlated with tumorigenicity in vivo. Most of the mammary tumor cell lines appeared to produce C-type virus. Only one, a C3H derivative, appeared to respond to stimulation by glucocorticoids with the enhanced production of B-type virus. Analysis of the growth properties exhibited in culture by transformed mammary epithelial cells revealed marked differences from those previously reported for transformed fibroblasts. (39 Refs) (Author Abstract)

364. HETEROGENEITY OF TUMOR CELLS IN MOUSE MAMMARY NEOPLASMS (MEETING ABSTRACT).

Dexter DL, Kowalski HM, Fligiel Z, Heppner GH
Dept of Medicine, Roger Williams General Hosp., Brown Univ., Providence, RI 02912
Proc Am Assoc Cancer Res; 18:45 1977

This study focuses on the heterogeneity of tumorigenic cell types within spontaneously arising mouse mammary tumors. Three cell lines were obtained from a morphologically heterogeneous primary culture of a single randomly chosen mammary adenocarcinoma arising in a strain BALB/cfC3H mouse. Two of the lines (66, 68-H) were obtained by a differential trypsinization cloning technique; the third (67) resulted from plating the primary cells on gelatinized dishes. Each line has a unique morphology as shown by light and scanning electron microscopy. The 66 line continues to give mixed cell types in subsequent passaging; the 67 cells always grow as a homogeneous population of elongated cells arranged in a net-like lattice. The 68-H line maintains its epithelial appearance, although the population it was cloned

from (68-D) now contains fibrobiastic cells. The lines vary in growth rate and plating efficiency in agar and on plastic. They also show marked differences in amount of mammaty tumor virus surface antigen, as shown by fluorescent antibody staining. Most important, all 3 lines and 68-D are tumorigenic in syngeneic hosts, producing histologically distinct tumors. Thus there is no unique cell type responsible for neoplastic growth; rather, the heterogeneity observed in culture reflects the presence of at least three distinct tumor cell types. (Author Abstract)

365. CHARACTERIZATION OF MOUSE MAMMARY TUMOR VIRUSES FROM PRIMARY TUMOR CELL CULTURES I: IMMUNOLOGIC AND STRUCTURAL STUDIES.

Kimball PC, Boehm-Truitt M, Schochetman G, Schlom J
Natl. Cancer Inst., Bethesda, MD 20014
J Natl Cancer Inst; 156(1):111-117 1976

Primary cell cultures of mammary tumors from RIII, GR, DD, BALB/cfC3H, and BALB/c mice were prepared by trypsin-EDTA dissociation of tumors in order to characterize, structurally and immunologically, the viruses produced by such cell cultures. Characterization was accomplished by radioimmunoprecipitation assays for mouse mammary tumor viruses (MuMTV) and murine leukemia virus (MuLV) antigens, and by analysis of virus proteins and glycoproteins by gel electrophoresis. Cultures from these strains predominantly contained cells of epi.helial morphology which formed three-dimensional domelike structures. Cultures from RIII, GR, DD, and BALB/cfC3H tumors produced extracellular type-B MuMTV, either in the absence of detectable type-C virus or with less than 1% contamination with type-C virus. Only BALB/c cultures produced MuMTV with as much as 3% contaminating MuLV. High levels of MuMTV surface antigen were also found in soluble form in culture supernatants. Virus polypeptide analyses showed that the RIII, BALB/cfC3H, DD, and BALB/c viruses all contained polypeptides characteristic of MuMTV. The authors conclude that primary cultures of mammary tumor cells make available a source of purified MuMTV antigens, structural proteins, and nucleic acids for comparative studies of MuMTV from various mouse strains.

366. CHARACTERIZATION OF MOUSE MAMMARY TUMOR VIRUSES FROM PRIMARY TUMOR CELL CULTURES. II. BIOCHEMICAL AND BIOPHYSICAL STUDIES.

Kimball PC, Michalides R, Colcher D, Schlom J
Natl. Cancer Inst., Bethesda, MD 20014
J Natl Cancer Inst; 56(1):119-124 1976

Primary mammary tumor cultures of RIII, GR, DD, BALB/c, and BALD/cfC3H mice were examined for mouse mammary tumor virus (MuMTV) production and the components of these viruses were characterized biochemically and biophysically. Levels of production of 12 to 32 ug virus protein/day/75 cm culture flask could be maintained for 30 to 50 days with daily virus harvests. The viruses from tumor cell cultures of these mouse strains contained DNA polymerase with a strong preference for Mg11 over Mn11 as the divalent cation, a characteristic of DNA polymerase of MuMTV from mouse milk. These viruses from tumor cell cultures were excellent sources of MuMTV ^{3}H-complementary DNA (complexed to 60 to 70S RNA) and radioactive 60 to 70S RNA, sufficiently free of contaminating murine leukemia virus nucleic acids, that can be used in molecular hybridization experiments. The effects of several culture parameters on MuMTV production were also studied. These experiments, combined with previous immunologic and structural studies, show that primary cultures of mammary tumor cells are useful sources for comparative studies of MuMTV from several mouse strains.

367. CULTIVATION AND CHARACTERIZATION OF BALB/CFC3H MAMMARY TUMOR CELL LINES.

Yagi MJ
Cancer Res. Lab., U. California, Berkeley
J Natl Cancer Inst; 51(6):1849-1860 1973

Cell lines and sublines initiated from BALB/cfC3H mammary adenocarcinomas exhibited varying morphologies during the 15- to 21-month culture periods. Two epithelial cell lines, FUKU and MJY, continued to form the hemicysts and mounds characteristic of primary cell cultures. Subline MJY-alpha did not form these structures. Instead, the cells varied from polygonal to fusiform within each passage level and, when confluent, the monolayers continually released viable cells into the culture fluid. When introduced into isogeneic hosts, FUKU rapidly established adenocarcinomas with acinar areas, though MJY-alpha yielded only slow-growing carcinosarcomas. 3H-uridine incorporation revealed the constant release of virions from the cell lines and subline. Immunodiffusion assays of virus purified from the culture fluids indicated that FUKU released a mixture of virions containing both mammary tumor virus (MTV) and murine leukemia virus (MuLV) antigens; MJY-alpha virions, on the other hand, were positive for only MTV antigens. Electron microscopic examination of the cell lines and purified virions substantiated this finding. Immunofluorescence detected a shift in the localization of MTV antigens in fixed cell layers of long-term cultures. With increasing passage levels, the cytoplasmic fluorescence typical of primary cultures was replaced by a cell membrane-associated staining pattern. By the fourth to sixth passage level, only cell-surface fluorescence was observed with use of anti-MTV antisera.

368. AN ESTABLISHED RIII MOUSE MAMMARY TUMOR CELL LINE; KINETICS OF MAMMARY TUMOR VIRUS (MTV) PRODUCTION (MEETING ABSTRACT).

Lasfargues EY, Kramarsky B, Sarkar NH, Lasfargues JC, Moore DH
Inst. Med. Res., Camden, N.J.
Proc Soc Exp Biol Med; 139(1):242-247 1972

A cell line was established from a soft spontaneous mammary tumor which occurred in an RIII mouse. The cell line, RIII-MT, was epithelial. Thin sections of the cultures prepared at 2-3 month intervals during the three yr of cultivation have consistently shown the presence of intracytoplasmic A-type particles and also B-type particles budding from the cell membrane. C-type particles associated with the leukemia-sarcoma system have not been found. Mammary tumor virus (MTV) antigen was detected in the third lactation milk of 34 out of 42 C57BL female mice inoculated with culture fluids. Several of these animals developed mammary tumors; none developed leukemia. Inoculation of 4 X 106 RIII-MT cells into newborn RIII mice resulted in infiltrating carcinomas at the site of injection. The MTV produced at the cell surface of RIII-MT cells was not spontaneously released. Harvest of the virions was obtained by cell dispersion with trypsin followed by storage for seven days at 4 C. After refrigeration, the virus retained its full infectivity.

369. REPLICATION OF MAMMARY TUMOR VIRUS IN TUMOR CELL CULTURES: DEPENDENCE OF HORMONE-INDUCED CELLULAR ORGANIZATION.

McGrath CM
Dept. Bacteriol. Immunol., U. California, Berkeley
J Natl Cancer Inst; 47(2):455-466 1971

A study was made to determine the effect of insulin, hydrocortisone and prolactin on mammary tumor virus (MTV)

replication in chronically virus-infected mouse mammary epithelium. When cultures of MTV-infected mammary adenocarcinoma cells from BALB/cfC3H female mice were cultivated in media supplemented with 7% fetal calf serum but without hormone, media were virtually inactive in the de novo production of MTV. Adding insulin resulted in release of MTV; maximum induction, usually a 10-15-fold increase over MTV production in non-insulin-treated cultures, required 10 microg/ml of insulin. Maximum release of MTV virions occurred between 36-48 hr after addition of insulin. Recovery of MTV from insulin-treated cultures was correlated with the appearance of 3-dimensional cellular structures ("domes"). The epithelioid cells confined to these domes were the primary foci of MTV production. Hydrocortisone stimulated MTV production in BALB/cfC3H cells; MTV production increased maximally between 12-24 hr after addition of hydrocortisone. Domes were also associated with MTV release in hydrocortisone-treated cultures. Stimulation of MTV production and dome development by hydrocortisone required pretreatment of tumor cells with insulin. Hydrocortisone acted without mitogenic stimulation of cells and did not modify kinetics of MTV replication per infected cell. Prolactin did not measurably influence MTV production.

370. MARKERS TO DISTINGUISH NORMAL AND NEOPLASTIC MAMMARY EPITHELIAL CELLS IN VITRO: COMPARISON OF SATURATION DENSITY, MORPHOLOGY AND CONCANAVALIN A REACTIVITY.

Voyles BA, McGrath CM
Michigan Cancer Foundation, Detroit, Michigan, USA
Int J Cancer; 18(4):498-509 1976

Normal and premalignant mouse mammary epithelial cells can be prepared in high yields by collagenase dissociation of minced glands followed by a brief, differential centrifugation to remove contaminating fibroblasts and fat cells. The major difficulties in preparing pure cultures in quantity are 1) incomplete dissociation of gland material, and 2) cell death during enzymatic digestion. These problems are eliminated by careful selection of collagenases for dissociation. Normal and premalignant mammary epithelial cells are morphologically indistinguishable from malignant mouse mammary epithelial cells in primary monolayer cultures. In addition, the growth rates and saturation densities achieved by normal mammary epithelial cells are indistinguishable from those of malignant mammary epithelial cells in primary culture. In both cases, a monolayer of cells is preserved with no evidence of focal overgrowth. Malignant adenocarcinoma mammary cells can however be distinguished from normal mammary epithelial cells by virtue of differences in their surface interactions with concanavalin A. A hemadsorption assay using Con-A-coated erythrocytes was the most sensitive indicator for these differences. In hemadsorption assays malignant mammary epithelial cells were half-maximally reactive with 2.5 ug/ml concanavalin A, while normal cells were completely unreactive even at concanavalin A concentrations five-times higher. Premalignant mammary epithelial cells were as reactive as malignant mammary epithelial cells in the hemadsorption assays. Hemadsorption of malignant cells was observed in primary and secondary cultures of epithelium as well as in cell lines. Malignant cells forming mammary adenocarcinomas were as highly reactive as malignant cells forming scirrhous carcinomas. Malignant cells not releasing mammary tumor virus (MuMTV) were as reactive as cells releasing that virus. Adsorption of concanavalin-A-coated erythrocytes to normal mammary epithelial cells could be induced by brief treatment of cell monolayers with hyaluronidase. Exposure of active sites was not affected with either trypsin or collagenase. Our results show that while the growth of malignant cells does not serve to distinguish them from normal cells in monolayer culture, surface changes do exist which can be identified by differences in concanavalin A reactivity. Since the earliest transformants identifiable in vivo (premalignant) have undergone conversion of the surface marker, concanavalin-A-mediated hemadsorption provides a sensitive measure for mammary epithelial cell transformants in vitro. (Author Abstract)

371. PRIMARY EPITHELIAL CELL DOME CULTURE OF MOUSE MAMMARY TUMORS.

Young LJ, Cardiff RD, McGrath CM
Dept. Pathology, Sch. Medicine, Univ. California, Davis, CA 95616
Tissue Culture Assoc Manual ; 1(3):161-164 1975

The initiation and maintenance of dome cultures from mouse mammary tumor epithelial cells are described. Primary cultures produced mouse mammary tumor virus that was harvested at maximum levels for 2-4 wk after culture initiation. The authors conclude that the initiation and maintenance of the dome culture depend on four factors: (1) proper tumor selection, (2) the dissociation technique, (3) proper plating density, and (4) supplementation with hormones and fetal bovine serum. This type of primary cell culture may be useful for the study of epithelial cells from other organs and may be applicable to problems of epithelial cell differentiation. (4 refs)

372. "DOMES", PERIODICALLY EXPANDING AND COLLAPSING SECRETORY STRUCTURES IN CELL CULTURES OF MOUSE MAMMARY TUMORS.

Visser AS, Prop FJ
Dept. Path., Wilhelmina Gasthuis, U. Amsterdam, The Netherlands
J Natl Cancer Inst; 52(1):293-295 1974

Monocellular suspensions made from primary mammary tumors of C3H mice bearing the mammary tumor virus (MTV) formed domes approximately 1 day after the cultures formed confluent epithelial monolayers. These domes were studied using time-lapse micro-cinematographic phase contrast movies. The domes expanded and collapsed 1-4 times every 2 hours in untreated cultures and cultures treated with: insulin, prolactin, and cortisol; insulin, progesterone, and cortisol; and progesterone and cortisol. During expansion, the dome gradually filled itself with fluid following the initial release of a small area of cells from the underlying polystyrene bottom. The adherent cells at the margin often suddenly loosened and became part of the dome surface structure. The growth of the dome continued for 30-120 minutes, after which the dome emptied itself within 2 minutes. For 4-15 minutes thereafter, the dome cells were barely discernible from the surrounding monolayer cells. Then the cycle repeated itself. New domes in time originated in places where a "quiescent" monolayer previously existed. In some domes during filling, certain solitary cells consistently remained attached to the bottom. The pulsations in the domes are most easily explainable in terms of secretory activity of the dome cells into the dome cavity followed by rupture of the intercellular connections when the tension in the dome became too high.

373. SUSPECTED PRENEOPLASTIC NATURE OF MAMMARY NODULES (HAN) DERIVED FROM ORGAN CULTURE.

Lin FK, Banerjee MR
Tumor Biology Laboratory, School of Life Sciences, University of Nebraska-Lincoln, Lincoln, NE. 68503
Proc Am Assoc Cancer Res; 16:91 1975

Previously, we reported that HAN can be induced by DMBA or MCA in organ culture of the entire mammary gland of C3Hf mice. The present studies centered around (1) induction of HAN in organ culture of mammary gland of MTV- and NIV-free BALB/c mice and (2) to test the tum-

origenic potential of these nodules. The entire mammary gland of the young virgin BALB/c mouse was treated with 1 ug DMBA or 5 ug MCA/ml medium for initial 24 hr of 6 day alveolar growth in culture with Insulin (I), Prolactin (Prl) and Aldosterone, incubated for another 6 days in medium with I+Prl+cortisol ; then cultivated with I alone for 11 days resulting to alveolar regression. HAN was observed in 30% of the carcinogen-treated glands (120) only. The presence of cortisol during DMBA treatment enhanced HAN induction and this effect appeared cell cycle related. Discrete HAN, containing milk-like material, were transplanted into "gland-free" mammary fat-pads of virgin hosts carrying a pituitary isograft. The grafted pituitary was removed after 10 weeks and 8 weeks later the animals were killed. Several microscopic tumor-like lesions were present in the HAN outgrowths but not in the normal mammary parenchyma. Histology of these lesions revealed ductal hyperplasia, metaplasia and possible foci of neoplastic growth. (Author Abstract)

374. PROLIFERATION OF PRENEOPLASTIC MAMMARY NODULE OUTGROWTH IN MAMMARY FAT PADS OF BALB/C MICE IN ORGAN CULTURE.

Mehta RG, Washburn LL, Young PN, Banerjee MR, Bern HA
Inst. Cellular Res., Sch. Life Sci., U. Nebraska, Lincoln
J Natl Cancer Inst; 52(3):1013-1017 1974

Fragments of a murine mammary tumor virus (m-MTV)-free outgrowth of a hyperplastic alveolar nodule (HAN) from a BALB/c mouse (D1 line) were transplanted into "gland-free" inguinal (fourth) mammary fat pads of BALB/c mice. Three weeks later, the whole mammary fat pad was removed and incubated in hormone-supplemented medium. Most of the outgrowth explants proliferated in the inguinal fat pad organ culture medium supplemented with the same hormones as are required for the in vitro growth of normal mammary gland; after 12 days, the nodule tissue filled over 50% of the fat pad. The extent of growth obtained within 12 days in organ culture was equivalent to that generally seen after 6 weeks in vivo. The rate of DNA synthesis in the explant corresponded with the growth pattern up to day 4; although DNA synthesis was reduced after this time, the explant continued to proliferate at a reduced rate up to 12 days. When the preneoplastic tissue was transplanted into already explanted fat pads, subsequent growth in vitro was not observed.

375. CHEMICAL CARCINOGEN-INDUCED HYPERPLASTIC NODULES IN WHOLE MAMMARY GLAND ORGAN CULTURE (MEETING ABSTRACT).

Wood BG, Washburn LL, Banerjee MR
Inst. Cell Res., U. Nebraska, Lincoln
Proc Am Assoc Cancer Res; 15:22 1974

This study involves induction of "transformation" of epithelial cells in whole mammary gland organ culture. The second mammary gland of virgin C3HfBALB/c mice were induced to full lobulo-alveolar growth within 5 days in organ culture with estrogen, progesterone, aldosterone, prolactin, growth hormone and insulin. Subsequent incubation with insulin alone caused regression of the alveoli. The gland resembled the involuted mammary gland in vivo. In carcinogenesis studies glands in complete medium were treated with DMBA (1.0 microg/ml) or MCA (5.0 microg/ml) for the initial 24-72 hr, then incubated in complete medium without carcinogens for 2-4 days. The glands were then regressed in insulin medium for 10 days. In carcinogen treated cultures alveolar nodules were numerous, 24% in DMBA and 26% in MCA treated glands. The average number of lesions per gland was 4.3 in DMBA and 4.6 in MCA. Lesions were virtually absent in the 54 controls. Histologically these lesions were similar to the preneoplastic mammary nodules induced by m-MTV, MCA or hormones. The results are the first demonstration of nodular transformation of mammary epithelium by chemical carcinogens in organ culture. The preneoplastic nature of these nodules is being examined by fat-pad transplantation in vivo.

376. PROPAGATION OF MOUSE MAMMARY TUMOR CELL LINES AND PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS IN A SERUM-FREE MEDIUM.

Bauer RF, Arthur LO, Fine DL
NCI Frederick Cancer Res. Center, Post Office Box B, Frederick, MD 21701
In Vitro; 12(8):558-563 1976

A serum-free (SF) medium was developed that supports the growth of several mouse mammary tumor cell lines and the synthesis of mouse mammary tumor virus (MMTV). Eagle's minimum essential medium with Earle's balanced salts was used as the basal medium to which were added sodium bicarbonate and a serum substitute consisting of a mixture of amino acids, vitamins, inorganic salts, and buffers. Five different mouse mammary tumor cell lines were propagated in the SF medium. Growth characteristics, such as logarithmic growth, cell population increase, protein production, and days to confluency, in SF medium were comparable to those in serum-containing medium. Cells grown in SF medium could be subcultured at high split ratios and passaged continuously after adaptation to SF medium. Significantly higher levels of MMTV expression, as detected by RNA-dependent DNA polymerase assays, occurred in the SF medium subsequent to dexamethasone stimulation than in serum-containing medium. Studies involving mammary tumor cell cultures that use SF medium can provide greater standardization of culture medium by avoiding the introduction of variables and possible exogenous contaminants associated with serum. (12 Refs)

377. SCANNING ELECTRON MICROSCOPY (SEM) OF MAMMARY TUMOR VIRUS (MTV) BUDDING FROM C3H MOUSE MAMMARY TUMOR CELLS IMMUNOLOGICALLY LABELED WITH TOBACCO MOSAIC VIRUS (TMV) (MEETING ABSTRACT).

Nemanic MK, Carter DP
Cancer Res. Lab., Univ. California, Berkeley, CA 94720
Fed Proc; 33(3):754 1974

Primary mammary tumor cells grown in vitro under conditions allowing mammary tumor virus (MTV) secretion were fixed in formaldehyde and incubated successively with hapten-modified anti-MTV, anti-hapten antibody and hapten-modified tobacco mosaic virus (TMV); the hapten used was P-azophenyl-beta-lactoside (Lac). The labeled cells were post fixed in glutaraldehyde, critical point dried and platinum coated. In scanning and transmission electron microscopy, TMV was observed only attached to microvilli, 100-nm virus particles and budding particles; controls substituting Lac-modified normal rabbit Ig for Lac-anti-MTV were negative (less than 5% labeling). Lac-modified erythrocytes were labeled with Lac-TMV only if treated first with anti-Lac-antibody; antibody to a closely related hapten (O-azophenyl-beta-galactoside) gave no labeling. We have not observed label on tumor cells not displaying microvilli. Adjacent cells with similar dense clusters of microvilli often showed 20- to 50-fold differences in label density. The non-microvillar surfaces of densely labeled cells bore few TMV particles. TMV attached end on and was easily visible at low magnification (3000X). Heavily labeled cells could be found even with the Lac-anti-MTV diluted 10 times (0.06 mg/ml).

378. RELEASE OF LEUKEMIA C PARTICLES FROM MURINE CELL LINES INFECTED WITH BITTNER VIRUS-CONTAINING INOCULA.

Lasfargues EY, Pillsbury N, Lasfargues JC, Moore DH
Inst. Med. Res., Camden, N. J.
Cancer Res; 30(1):167-168 1970

Embryo and mammary tissue cultures of C57BL/Haag mice were inoc with milk from RIII mice, B particles from RIII milk or extracts of a tumor induced in a C57BL mouse by RIII milk. Inoc caused continuous growth of all cell lines with no distinct morphological differences from controls in the early mo, but changes were noted after 3-4 mo. Electron microscopic studies showed abundant type C virus particles in all inoc cell lines, especially cell cultures inoc with tumor extract, and rarely in control cultures. Serological analysis indicated that the cell lines are positive for complement fixation with polyvalent leukemia antiserum and for immunofluorescence with leukemia antiserum, but negative with mammary tumor virus antiserum inj. (ip or sc) into BALB/c and C57BL mice induced sarcomas at the site of inj for all 3 cell lines.

IX. CELL INFECTIVITY STUDIES OF MuMTV

379. INFECTIVITY AND ONCOGENICITY OF THE MOUSE MAMMARY TUMOR VIRUS IN TISSUE CULTURE.

Lasfargues EY, Sheffield JB
Inst. Medical Res., Camden, NJ
J Microsc Biol Cell; 26(1):29-34 1976

Cat kidney cells and lung cells from mink embryos were infected in tissue culture by the mouse mammary tumor virus (MuMTV). Mouse milk was the best source of purified virions. The target cells could be inoculated equally well in suspension or on monolayers, but a large number of cells should be in the S phase. Following inoculation, the cells had the same morphology, growth rate, and behavior as the control cells not exposed to MuMTV. That the inoculated cells were actually infected and producing virus was demonstrated by electron microscopy, in which virions were seen in the process of budding from the cell, and membrane immunofluorescence. The ip injection of 3 x 10^7 cat virus-producing cells into female C57BL mice resulted in the infection of 9/20 animals. Because of nonhistocompatibility, the cat cells did not grow in the mouse peritoneal cavity, but the virus replicated and eventually elicited a mammary tumor 9 mo after inoculation. Normally, C57BL mice do not develop mammary tumors. These results should be considered in any attempt to analyze the mechanisms of mammary carcinogenesis. It is evident that the virus is essential, since mammary tumors occur whenever it is inoculated into susceptible mice, but cell transformation appears to depend on a second factor, perhaps one of a genetic nature. (16 refs)

380. MURINE MAMMARY TUMOR VIRUS INFECTION OF MOUSE MAMMARY EPITHELIAL CELLS IN VITRO (MEETING ABSTRACT).

Vaidya A, Lasfargues EY
Inst for Medical Res, Camden, NJ 08103
Proc Am Assoc Cancer Res; 18:240 1977

Until recently, it was not possible to infect cultured cells with murine mammary tumor virus (MuMTV), making it difficult to develop in vitro systems to carry out careful virological investigations. Although we have now been able to infect non-murine cells with MuMTV, appropriate studies on the virus-target cell interaction can only be carried out in mouse mammary cells. Here we report the successful MuMTV infection of an epithelioid cell line derived from mammary glands of C57BL mouse (C57MG). Although uninfected C57MG cells contain endogenous MuMTV proviral DNA, we were not able to detect any MuMTV RNA in these cells by nucleic acid hybridization. After the infection with MuMTV, C57MG cells acquired additional MuMTV proviral DNA sequences. Kinetics of hybridization between RNA isolated from infected C57MG cells and MuMTV cDNA revealed a high level of MuMTV RNA synthesis; about 1100 copies of MuMTV RNA were present per infected C57MG cell on an average. The accumulation of MuMTV RNA in these cells was stimulated by dexamethasone. About 2 x 10^6 MuMTV virions are released by these cells per ml of the culture fluid in 48 hrs; also, electron microscopic observations revealed budding B-particles. Our preliminary results indicate that logarithmic dilution of infecting MuMTV causes logarithmic reduction in the average number of MuMTV RNA molecules present per infected cell. (Author Abstract)

381. EXPERIMENTAL INFECTION OF NON-MURINE CELLS BY MURINE MAMMARY TUMOR VIRUS (MEETING ABSTRACT).

Howard DK, Colcher DM, Teramoto YA, Young JM, Schlom J
Meloy Lab Inc., Springfield, VA 22151
Proc Am Assoc Cancer Res; 18:108 1977

Established cell lines of feline and mink origin have been productively infected with murine mammary tumor viruses (MMTVs) from three different strains of mice thus confirming and extending the reports of Lasfargues et al. The virus being released by these cells competes completely in radioimmunoassay for the major virion glycoprotein of MMTV (gp52), thus demonstrating that antigenic determinants of gp52 are viral coded. Competition hybridization studies have shown that the 60-70S viral RNAs of MMTVs released by feline cells contain all the sequences found in RNA from MMTV synthesized by murine cells. The virion buoyant densities in sucrose and cesium chloride, the virion sedimentation coefficient, divalent cation requirement of the virion DNA polymerase, and virion morphology of MMTVs synthesized in heterologous cells are identical to those of MMTVs grown in murine cells. Cultures of MMTV-infected feline cells have continuously released 0.1-1.0 mug of virus per $75cm^2$ flask per day during a 40 week observation period. No detectable feline or murine type C viruses were being produced by these cultures. Studies are in progress to further characterize the nucleic acids and proteins of various MMTVs grown in heterologous cells. (Author Abstract)

382. MURINE MAMMARY TUMOR VIRUS: CHARACTERIZATION OF INFECTION OF NONMURINE CELLS.

Vaidya AB, Lasfargues EY, Heubel G, Lasfargues JC, Moore DH
Institute for Medical Research, Camden, New Jersey 08103
J Virol; 18(3):911-917 1976

Murine mammary tumor virus (MuMTV) was used to productively infect feline and mink cells. MuMTV "proviral" DNA could be detected in the infected cells by molecular hybridization using radioactive MuMTV complementary DNA as a probe. Kinetic analysis of MuMTV proviral DNA synthesis after infection showed that maximum MuMTV DNA synthesis was achieved by 8 h; however, this was followed by a decline in detectable proviral DNA and eventual stabilization at a lower level. MuMTV synthesis in feline cells was greatly stimulated by the synthetic glucocorticoid, dexamethasone. On the other hand, MuMTV synthesis in mink cells was relatively at a much higher level in absence of dexamethasone and the stimulation with dexamethasone was

not as marked as in the case with infected feline cells. Thermal denaturation of hybrids between MuMTV complementary DNA and infected mink cell RNA revealed no difference from homologous hybrids. (Author Abstract)

383. CELL TRANSFORMATION AND MOUSE MAMMARY TUMOR VIRUS.

Lasfargues EY, Lasfargues JC, Robinson CS
Robinson Inst. Medical Res., Camden, NJ 08103
In Vitro; 12(4):316-317 1976

Two cell lines, one derived from cat kidney cells (CRFK-F2), the other from mink embryos (CCL-64) have been successfully infected with a mammary tumor virus (MuMTV) isolated from RIII mouse milk and purified by velocity centrifugation on a 0-25% Ficoll density gradient. Infection was done at 37 C by direct contact with the cells either in suspension or in monolayer. Replication of the virus was detected 2 wk later by electron microscopy and by immunofluorescence. Over a year's observation, the infected cells have continuously released virus in their supernatant but remained morphologically indistinguishable from the controls not exposed to the virus. The modal number of chromosomes of 38 for cat cells and 29 for the mink remained unchanged, as did the doubling time of about 20 hr. When seeded in soft agar, cat kidney cells initiated small colonies 5 to 10 cells big whether or not they had been infected with MuMTV. Mink cells remained contact-inhibited at all times, their single layer shedding necrotic cells. The lack of significant changes in morphology, chromosome number, and growth rate in cells unquestionably infected by MuMTV is interpreted as a lack of transformation. It is concluded that MuMTV does not necessarily induce neoplasia in cells where it replicates.

384. INFECTION OF MINK EMBRYONIC CELLS WITH THE MOUSE MAMMARY TUMOR VIRUS.

Lasfargues EY, Lasfargues JC, Moore DH
Institute for Medical Research, Camden, NJ 08103
Proc Am Assoc Cancer Res; 17:33 1976

An epithelial cell line (CCL-64) derived from the trypsinized lungs of mink embryos, was infected with a mouse mammary tumor virus (MuMTV) purified from RIII mouse milk. The procedure used was described for the infection of cat kidney cells (Lasfargues et al, Cancer Res. Jan. 1976). Infection was confirmed by electron microscopy and immunofluorescence, using a rabbit serum against RIII MuMTV. Milk cells have also been infected with MuMTV from A mouse milk and with a tissue culture virus from a BALB/cfC3H cell line. Following infection with RIII MuMTV, it was found: 1) that all cells can adsorb some virus on their surfaces but that few become coated with it; 2) that only a fraction of the inoculated cells synthesize virus 1 week after inoculation. It is concluded: 1) that all the virus particles in the inoculum are not infective; 2) that some cells are more sensitive than others to MuMTV. Cloning these sensitive cells might be a first step towards an in vitro assay for MuMTV. (Author Abstract)

385. BRIEF COMMUNICATION: IN VITRO SUSCEPTIBILITY OF MINK LUNG CELLS TO THE MOUSE MAMMARY TUMOR VIRUS.

Lasfargues EY, Vaidya AB, Lasfargues JC, Moore DH
Department of Cytological Biophysics, Institute for Medical Research, Camden, N.J. 08103.
J Natl Cancer Inst; 57(2):447-449 1976

Lung cells from mink embryos were infected in vitro with a purified mammary tumor virus isolated from RIII mouse milk. Specific virus antigen at the cell surface was detected by membrane immunofluorescence; B-type virions budding from the cell membrane were seen by electron microscopy. Nucleic acid hybridization confirmed replication and specificity of the virus produced. (Author Abstract)

386. OBSERVATIONS ON THE INFECTIVITY OF THE MOUSE MAMMARY TUMOR VIRUS IN MINK LUNG CELLS (MEETING ABSTRACT).

Lasfargues EY, Vaidya AB, Lasfargues JC, Moore DH
Inst. Medical Res., Camden, NJ 08103
J Cell Biol; 70(2/Part2):81a 1976

Cat kidney cells and mink lung cells from two established epithelial cell lines have been found susceptible to infection by the mouse mammary tumor virus (MuMTV). Milk from RIII mice yields an average of 375ug viral proteins per ml as determined by Lowry analysis. Following filtration through a 0.45u Millipore filter, 2×10^{11} virions, equivalent to 180ug viral proteins, were resuspended in 1 ml of Eagle's medium containing 4ug polybrene to inoculate 10^6 mink cells. Two weeks after inoculation and following two split transfers of the cell population, membrane-immunofluorescence tests detected 20 to 30% virus-producing cells. These were characterized by a strong peripheral fluorescence. The number of positive cells increased in the next three months up to a maximum of 70% then declined gradually in another three months until virus expression could barely be found. Nucleic acid hybridization of the cell DNA with a radioactive DNA complementary to MuMTV-RNA (cDNA) has shown that even though new virions were not synthesized, the proviral DNA was still present in the cells. It is assumed that inhibitors have interrupted the transcriptional mechanism of the virus, a situation in many ways comparable to that of the C57BL mouse cells which do contain the MTV genome but nevertheless do not synthesize virus or become neoplastic.

387. EXPERIMENTAL INFECTION OF A CAT KIDNEY CELL LINE WITH THE MOUSE MAMMARY TUMOR VIRUS.

Lasfargues EY, Lasfargues JC, Dion AS, Greene AE, Moore DH
Inst. Medical Res., Camden, N.J. 08103
Cancer Res; 36(1):67-72 1976

The cat kidney cell line, CRFK-F2, was inoculated in suspension and in monolayer culture with a purified mouse mammary tumor virus derived from RIII milk. A virus produced by the infected cells was identified by immunofluorescence, electron microscopy, and RNA-directed DNA polymerase assays; it was a B-type virion that did not cross-react with mouse or feline leukemia-sarcoma viruses, had spikes on its envelope, and also had a RNA-directed DNA polymerase reaction typical of mouse mammary tumor virus. The producing cells were identified as cat cells by means of chromosome number, cytotoxic assays, and isoenzyme migratory patterns. A standardized method for the in vitro inoculation of cat cells was described. The mouse mammary tumor virus was seen replicating in cells from another species, offering an opportunity to study the kinetics of infection of the virus.

388. DETECTION OF MOUSE MAMMARY TUMOR VIRUS IN CAT KIDNEY CELLS INFECTED WITH PURIFIED B PARTICLES FROM RIII MILK.

Lasfargues EY, Kramarsky B, Lasfargues JC, Moore DH
Inst. Med. Res., Camden, N. J.
J Natl Cancer Inst; 53(6):1831-1833 1974

A feline kidney cell line (CRFK-F2) was experimentally infected with B particles obtained by isopycnic banding of RIII mouse milk on a Ficoll gradient. Free B particles were found in the culture supernatants 3 months postinoculation; the overall dimensions of the virions as well as the length and spacing of the spikes were the same as those of murine mammary tumor virus (MuMTV). MuMTV antigen was then

detected by membrane immunofluorescence, with about 20% of the cells showing this specific antigen on their surfaces 1 yr after infection. Electron microscopy revealed formation of virions in microvilli and accumulation of specific antibodies on their surfaces. Idiogram and zymogram studies confirmed that the cultured cells were not of mouse origin. Active budding of MuMTV has not been detected in renewed attempts to infect these cells with RIII milk virus or an MuMTV from a BALB/cfC3H tumor cell line.

389. INFECTION OF CULTURED RAT HEPATOMA CELLS BY MOUSE MAMMARY TUMOR VIRUS.

Ringold GM, Cardiff RD, Varmus HE, Yamamoto KR
Department of Biochemistry University of California, San Francisco San Francisco, California 94143
Cell (Camb); 10(1):11-18 1977

A continuous line of buffalo rat hepatoma (HTC) cells has been successfully infected with mouse mammary tumor virus (MMTV) produced by the GR mammary tumor cell line. [illegible]iform infection required initial exposure of the HTC cells to greater than 10^5 MMTV particles per cell. The resultant chronically infected cell population was found to have stably acquired 20-30 copies of MMTV DNA. The infected cells contain viral RNA and express viral antigens; however, very few MMTV particles are released into the culture medium. In spite of the biochemical evidence for infection, we have not detected any alterations in the morphology or growth properties of the infected HTC cells. As is the case in mammary tumor cells, the intracellular concentration of viral RNA is strongly stimulated (50-150 fold) by the synthetic glucocorticoid, dexamethasone. Thus it appears that the mechanisms by which glucocorticoids regulate MMTV gene expression in mouse cells are maintained when this virus infects nonmurine cells. (Author Abstract)

390. MOUSE MAMMARY TUMOR VIRUS DNA IN INFECTED RAT CELLS: CHARACTERIZATION OF UNINTEGRATED FORMS.

Ringold GM, Yamamoto KR, Shank PR, Varmus HE
Department of Biochemistry University of California, San Francisco San Francisco, California 94143
Cell (Camb); 10(1):19-26 1977

Mouse mammary tumor virus (MMTV) DNA in chronically infected rat hepatoma cells is maintained in both the integrated and unintegrated state. Fractionation of DNA by the procedure of Hirt (1967) as well as by sedimentation through alkaline sucrose suggests that about two thirds of the viral DNA is associated with high molecular weight cell DNA. The remainder of the viral DNA is unintegrated and is present primarily as linear or open circular duplexes consisting of a genome-length strand complementary to the viral RNA ("minus" strand) and "plus" strands of subgenomic length. Approximately 20% of the unintegrated MMTV DNA is present as double-stranded, covalently closed circles (form I) with a molecular weight of 6×10^6 daltons. Form I viral DNA is found primarily in the nucleus, whereas the open forms are both nuclear and cytoplasmic. (Author Abstract)

391. EFFECT OF MAMMARY TUMOR VIRUS INFECTION ON IN VIVO OXIDATION OF GLUCOSE-1-14C AND GLUCOSE-6-14C IN C3H MICE.

Burki HR, Okita GT
Northwestern U. Med. Sch., Chicago, Ill.
Cancer Res; 31(12):1955-1961 1971

A two-part study was conducted to compare the rate of in vivo oxidation of glucose-1-14C and glucose-6-14C in C3H tumor-free and C3Hf (factor-free) virgin female mice of different ages, and to determine the effect of the presence of small foci of mammary tumor tissue on the in vivo metabolism of glucose-14C. Although no differences were observed between young mice of the two strains, C3H virgins older than 40 wk oxidized glucose-6-14C to 14CO2 at a faster rate than C3Hf virgins of the same age. In addition, C3H mice older than 40 wk had significantly lower body wt than the C3Hf controls. No age-dependent interstrain differences in the rate of glucose-1-14C oxidation were observed. Injection sc of an homogenate of a spontaneous mammary tumor which arose in a C3H mouse resulted in a significant reduction in body wt and an increase in glucose-6-14C oxidation in C3Hf but not C3H virgins. The tumor nodules grew progressively in the C3Hf but not in the C3H mice. These results imply that degradation of glucose by the glycolysis-Krebs cycle pathway, but not by the pentose shunt, was increased in aging and in tumor-bearing C3H virgin mice.

392. THE VIROLOGY OF CANCER: PENETRATION OF MATURE VIRUS PARTICLES OF BREAST CANCERS INTO VIRUS-PRODUCING CELLS IN VIVO.

Thomas JA, Hollande E, Henry M, Vilain C
Lab. Biol., U. Paris, France
C R Acad Sci D (Paris); 273(20):1888-1891 1971

An ultrastructural study of the in vivo transmission of virus particles of breast cancer in Swiss mouse mammary gland adenocarcinoma (both spontaneous and mammary tumor virus-induced) from cell to cell was made. It was found that penetration of virus particles through the apical and lateral walls of cancer cells is accomplished through the mediation of phagocytic vacuoles surrounding each viral particle. Both immature virus particles which seem to mature in phagocytic vacuoles, as well as extracellular mature particles participate in this penetration; while both mature and immature particles penetrate through the lateral cell wall. It appeared that the walls of phagocyte vacuoles surrounding the mature virus particles were being resorbed by the cytoplasm. Penetration is morphologically identical through both apical and lateral cell walls even though the lining and the physiologic properties of these walls are different. The phenomenon observed corresponds to one modality of horizontal virus transmission. The process in vivo is a superinfection because the virus- producing cells are already charged with virus particles. The relationship of this process to vertical genetic transmission is unresolved, as is the meaning of the observed exceptional and paradoxical presence of mature virus particles in cellular nuclei.

393. BIOLOGICAL ACTIVITY OF DIFFERENT ZONES OETAINED BY ULTRACENTRIFUGATION OF THE LACTEOUS FACTOR FROM PS STRAIN MICE PERFORMED ON FICOLL GRADIENTS.

Mouriquand J, Mouriquand C, Viala C
Biologie Cellulaire, Centre d'Etudes Nucleaires Grenoble, 38-La Tronche, France
Eur J Cancer; 6:115-124 1970

Cell free extracts of mammary tumors of the PS strain of mice were performed following Gross's technique and the extraction with fluorocarbon described by Moore. Bioactivity did not display a significant difference with the two methods. There was no loss of infectivity after storage at - 60C and - 195C. A significant loss of infectivity was only observed with cell free extracts performed following Gross's method and kept 24-48 hr at 4C. These extracts, samples of milk and of tissue culture media of mammary tumors, were ultracentrifugated on preformed density gradients of Ficoll. Bioassays with the zones thus obtained were performed on newborn mice of different strains: BALB/c, C3H/eB, 2nd PS. Infectivity was spread all over the gradient. Leukemias were observed in PS males and in one female of the strain BALB/c. These results are compared with similar studies of different authors. (Author abstract) (28 Refs)

X. MuMTV INTERFERENCE BY OTHER VIRUSES

394. LACK OF INTERFERENCE IN ANTIGEN PRODUCTION IN VITRO BETWEEN B-TYPE AND C-TYPE ONCORNAVIRUSES AS DETERMINED BY DOUBLE STAIN IMMUNOFLUORESCENCE.

Van Pelt FG, Houweling A, Aarssen AM, Bentvelzen P
Inst. Experimental Gerontology TNO, 151 Lange Kleiweg, Rijswijk, The Netherlands
Eur J Cancer; 12(4):321-323 1976

Cultures of mouse mammary tumor virus were examined to determine whether a cell could produce antigens of both B and C type viruses simultaneously and whether mutual interference existed. The results indicated that both types of oncornavirus could be detected simultaneously in the mammary tumor cultures. There was no statistical indication that either type of virus interfered with the production of antigens from the other.

395. PRESENCE AND TRANSMISSION OF MAMMARY TUMOR VIRUS AND LEUKEMIA VIRUS IN THE BALB/CFRIII MOUSE.

Squartini F, Bucciarelli E, Bolis GB
Med. Sch., U. Pisa, Italy
J Natl Cancer Inst; 53(1):137-150 1974

BALB/cfRIII is a high-mammary-tumor and high-leukemia strain of mice. The mammary tumor virus (MTV) and leukemia virus were demonstrated by biologic tests and electron microscopy in these mice. Experiments in which BALB/cfRIII mice were foster-nursed by C57BL mothers revealed that both MTV and leukemia virus are milk-transmitted. Tumors during the first 30 inbred generations (1291 mice) were unevenly distributed in the genealogic tree. Mammary tumors appeared more concentrated in some sublines and generations, and leukemia was more concentrated in others. The descendants of parents with mammary tumors or leukemia showed, resp, higher incidences of mammary tumors or leukemias. A strong repulsion between mammary tumors and leukemias occurred in females. In all instances, the higher the mammary tumor incidence the lower the leukemia incidence, and vice versa. Several of the differences found were significant. These data suggest that, although a fairly good propagation of MTV and leukemia virus was concomitant during the first 30 generations of the BALB/cfRIII strain, there were at the same time several examples of selection, segregation, and repulsion between these two viruses or their respective tumors. The data indicate some kind of interference between MTV and leukemia virus during natural life.

396. TRANSMISSION AND EXPRESSION OF THE LEUKEMIA INDUCING AGENT IN BALB/CF(RIII) MICE.

Squartini F, Bucciarelli E, Bolis GB
Med. Sch. Univ. Pisa, Italy
Bibl Haematol; (39):345-456 1973

Occurrence of mammary tumors and lymphatic leukemia during 20 generations (1,145 mice) of the BALB/cf (RIII) strain is reported. A very strong repulsion between mammary tumors and leukemias was observed in females. Nevertheless, analysis of the distribution of these two-types of tumors through the genealogical tree suggests a good propagation of both mammary tumor virus (MTV) and leukemia virus. The observations support the hypothesis that reciprocal interference between MTV and leukemia virus occurs at the level of malignant cell transformation.

397. FUSION OF XC RAT SARCOMA CELLS INDUCED BY MURINE LEUKAEMIA VIRUS-INFECTED MOUSE MAMMARY TUMOUR CELLS. ABSENCE OF INTERFERENCE BY SIMULTANEOUSLY SYNTHESIZED MAMMARY TUMOR VIRUS.

Svec J, Links J
Cancer Res. Inst., Bratislava, Czechoslovakia
Neoplasma; 20(6):699-703 1973

C3H mouse mammary tumor primary cultures were cocultivated with XC indicator cells pretreated with DEAE dextran; multinucleated syncytia characteristic for the action of murine leukemia virus (MuLV) were formed. To determine whether mouse mammary tumor virus (MTV) induces similar cytopathic effects in XC cells, the correlation between plaque formation activity and the presence or MuLV and MTV antigens was examined at various intervals after the seeding of tissue cultures with C3H mouse mammary tumor cells. The plaque forming activities of type-C-positive and type-C-negative mouse mammary tumor cell lines were also compared. The presence of plaque forming activity in the C3H mouse mammary cultures indicated the presence of MuLV antigens in these cells. Weak positivity in the XC test was also obtained in a few cultures showing no MuLV antigens. The full expression of the MuLV genome continued in 28-day-old cultures of C3H mammary tumor cells, in which the replication of MTV was suppressed. Finally, continuously produced MTV in the CLL-51 mammary tumor cell line, as well as purified and highly concentrated MTV, failed to induce syncytia and plaque formation in the indicator cell line. MTV does not appear to contain the heat-labile envelope lipoprotein which serves as the mediating factor in the MuLV-induced XC cell fusion. In addition, MuLV replicates independently from the expression of the MTV genome in mouse mammary tumors growing in vitro.

XI. STUDIES OF INTRACYTOPLASMIC A-PARTICLES

398. INTRACYTOPLASMIC A PARTICLES: MOUSE MAMMARY TUMOR VIRUS NUCLEOPROTEIN CORES?

Smith GH, Wivel NA
Natl. Cancer Inst., Bethesda, Md.
J Virol; 11(4):575-584 1973

A rapid method for the isolation of intracytoplasmic A particles, the putative intracellular nucleoprotein cores of mouse mammary tumor virus (MTV), is presented. Spontaneous C3H/He mouse mammary tumors and transplantable mouse Leydig cell tumor were used as source material. Large aggregations of intracytoplasmic A particles were separated from cellular contaminants on discontinuous sucrose gradients and subsequently further purified by isopycnic banding in linear sucrose gradients. The purified particles were solubilized in sodium dodecyl sulfate, and the structural proteins were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Purified mouse mammary tumor virions were solubilized, and their proteins were analyzed in the same way. Comparison of co-electrophoretic gels indicated a lack of correlation in the molecular size of the major structural proteins in intracytoplasmic A particles and MTV. The three major proteins of the A particles were calculated to be 80,000; 35,000; and 20,000 daltons. Five major polyacrylamide gel electrophoresis bands were obtained with purified MTV; these were 90,000; 69,000; 55,000; 37,000; and 27,500 daltons. These results suggest the need for the reexamination of the current tenet that intracytoplasmic particles present intracellular MTV nucleoprotein cores.

399. LOCALIZATION OF MOUSE MAMMARY TUMOR VIRUS ANTIGEN ON INTRACYTOPLASMIC A PARTICLE STRUCTURAL POLYPEPTIDES. (MEETING ABSTRACT).

Smith GH
Lab of Molecular Biology, Natl Cancer Inst, Bethesda, MD 20014

Proc Am Assoc Cancer Res; 18:126 1977

This study was designed to test the validity of the hypothesis that intracytoplasmic A particles (CAP) represent intracytoplasmic MMTV core precursors. Exposure of CAP to trypsin prior to SDS-polyacrylamide gel electrophoresis has been shown to quantitatively convert all CAP structural proteins to polypeptides whose electrophoretic mobilities are similar to MMTV core proteins p^{27}, p^{14} and p^{10}, at the same time preserving MMTV p^{27} antigenic determinants. Our recent study shows that this conversion is dependent upon the morphologic integrity of CAP ie, if CAP are disrupted either physically or chemically, tryptic hydrolysis results in the loss of MMTV p^{27} antigen and the SDS polyacrylamide polypeptide, which is co-electrophoretic with MMTV p^{27}. Concentration of CAP p^{82} by differential solubilization or by direct elution from polyacrylamide gels and subsequent analysis by immunodiffusion demonstrated that this CAP structural protein is a precursor to MMTV p^{27}. These results are consistent with the hypothesis that intracytoplasmic A particles are structural precursors to MMTV virion cores possessing as yet incompletely processed virion structural proteins. (Author Abstract)

400. MOUSE MAMMARY TUMOR VIRUS POLYPEPTIDE PRECURSORS IN INTRACYTOPLASMIC A PARTICLES.

Smith GH, Lee BK
Natl. Cancer Inst., Bethesda, Md. 20014

J Natl Cancer Inst; 55(2):493-496 1975

Intracytoplasmic A particles were analyzed by immunodiffusion and sodium dodecyl sulfate -polyacrylamide gel electrophoresis (SDS-PAGE) before and after enzymatic cleavage with trypsin. The particles were purified from transplantable Leydig cell tumors. Mouse mammary tumor virus (MMTV) was isolated from C3H-Avy/He mammary tumors by sequential rate zone sedimentation in two linear gradients. A common antigen in A particles was detected by antisera prepared against this virus and against a purified MMTV core polypeptide (p28) and purified intracytoplasmic A particles. Despite this correlation, no SDS-polyacrylamide band migrating at p28 was observed in purified intracytoplasmic A particles. However, after incubation with trypsin (1.25 microg/100 microg A particles protein, 30 min, 37 C), A particles subjected to SDS-PAGE produced only two polypeptide bands. They were observed at p28 and p15-10. Ouchterlony analysis of the trypsin-cleaved A particles revealed no alteration in the antigenicity of the particles. These results suggested that some structural components of intracytoplasmic A particles are polypeptide precursors of MMTV core proteins.

401. IDENTIFICATION OF MOUSE MAMMARY TUMOR VIRUS (MMTV) POLYPEPTIDE PRECURSORS IN INTRACYTOPLASMIC A PARTICLES (MEETING ABSTRACT).

Smith GH, Lee BK
NCI, Bethesda, MD 20014

J Cell Biol ; 67(2/Part2):407a 1975

Intracytoplasmic A particles (CAP) are presumptive intracellular precursors of MMTV nucleoprotein cores. At least one common antigen between purified CAP and MMTV has been detected by immunodiffusion, however, comparison of CAP and MMTV proteins by SDS-polyacrylamide gel electrophoresis (PAGE) failed to show any similarity in the molecular wt of their respective solubilized structural proteins. Five major structural proteins have been identified in MMTV; gp52, gp36, p28, p14, and p10. The 52,000 and 36,000 components are glycoproteins located on the virion surface, p28, p14, and p10 have been designated as nucleoid or core proteins. None of these were observed in CAP SDS PAGE preparations. A possible explanation of this is that cleavage of the existing CAP structural proteins occurs during MMTV maturation (budding) at the cell membrane. Pre-treatment of intact CAP with trypsin, quantitatively converted all CAP SDS-polypeptides to p28 and p15-10. Immunodiffusion demonstrated an antigen in CAP before and after trypsin treatment which was identically precipitated by anti-MMTV, anti-CAP, and monovalent anti-MMTV p28, suggesting that CAP p28 (post-trypsin) was the result of cleavage of precursor structural polypeptides in CAP containing MMTV p28 antigenic specificity. Evidence that CAP p15-10 (post-trypsin) was not related to the MMTV p28 antigenically was provided by experiments where CAP was treated with 0.2M dithiothreitol (DTT) prior to centrifugation. Ouchterlony analysis showed that this procedure separated the structural components of CAP containing the p28 specificity (DTT pellet) from the component (DTT supernatant) carrying the CAP p15-10 (post-trypsin). CAP p82 was the major SDS polypeptide found in the DTT pellet. CAP p20-16 was the major component solubilized by DTT. Digestion of CAP p20-16 with trypsin gave CAP p15-10 (post-trypsin).

402. RELATIONSHIPS BETWEEN INTRACISTERNAL TYPE A AND EXTRACELLULAR ONCORNAVIRUS-LIKE PARTICLES PRODUCED IN MURINE MOPC-460 MYELOMA CELLS.

Robertson DL, Yau P, Dobbertin DC, Sweeney TK, Thach SS, Brendler T, Thach RE
Dept. Biological Chemistry, Washington Univ., St. Louis, MO 63110

J Virol; 18(1):344-355 1976

Oncornaviruslike particles of the A (both intracisternal and intracytoplasmic) and B or C (extracellular) types are produced by murine MOPC-460 myeloma cells. A comparative study of intracisternal A and extracellular particles is described. Both types of particles contained an RNA-dependent DNA polymerase activity, traces of 35S and 70S RNA in addition to larger amounts of degraded RNA, and proteins of approximately 76,000 and 45,000 daltons. The 76,000-dalton proteins from intracisternal A and extracellular particles had the same cyanogen bromide peptides. Hybridization kinetic analysis indicated that the RNA's in the two particles were identical or very closely related and shared partial homology with Moloney leukemia virus RNA. In contrast, the particles appeared to have little or no relationship to murine mammary tumor virus, as judged by several different criteria. Electron microscope studies indicated that the extracellular particles arose from the budding of core components through the plasma membrane, and preliminary experiments indicated that they contained the same proteins as the intracisternal A particles. These results suggest that the intracisternal A and extracellular oncornaviruslike particles produced by MOPC-460 cells are closely related.

403. OBSERVATION OF INTRACYTOPLASMIC A-TYPE PARTICLES IN BABOON C-TYPE PARTICLE INFECTED CHIMPANZEE LUNG CELLS (SFRE:CL-1) (MEETING ABSTRACT).

Smith GC, Helmke RJ, Heberling RL, Kalter SS
Southwest Foundation Res. Education, San Antonio, TX

Tex Rep Biol Med ; 33(3):479 1975

Intracytoplasmic A-type particles were observed in a fetal chimpanzee lung culture (SFRE: CL-1) inoculated with babo-

on C-type virus. Crescent-shaped budding structures, immature particles, and mature particles typical of C-type virions were also observed. In thin section, spikes were not observed on budding intracytoplasmic A-type particles; however, some extracellular virions did possess "spike-like" structures on their surface. Unlike mouse mammary tumor virus or Mason-Pfizer monkey virus, eccentric nucleoids or 'theta-shaped' nucleoids were not observed. Attempts to reproduce the appearance of A-type virions under analogous conditions have thus far been unsuccessful. The source of these unique particles is obscure; whether they represent a new endogenous primate virus, a contaminant, or a morphological variation of C-type virus infection in currently under investigation.

404. ELECTRON MICROSCOPE STUDIES OF MOUSE MAMMARY TUMOR VIRUS (MTV) WITH SPECIAL CONSIDERATION OF THE MECHANISM INVOLVED IN EXTRUSION OF A-PARTICLES FROM THE CELL.

Ruhland D, Fasske E, Fetting R, Themann H
Dept. Med. Ultrastructural Res., U. Munster, Germany
Z Krebsforsch; 79(4):309-318 1973

Electron microscope studies were made of mammary tumors which developed spontaneously in up to 15% of female NMRI mice. A-particles were found only within the cell, while B-particles were present both in cytoplasmic vacuoles and in extracellular spaces. In actively secreting cells it was demonstrated that A-particles were extruded from the cells and matured into B-particles. Many A-particles formed in the Golgi apparatus. Protein secretion vacuoles developed nearby and migrated into these clumps of A-particles. A-particles then adhered to the membranes of protein-secretion vacuoles, and the secretion vacuoles, together with A-particles, migrated to the cell surface. Drops of protein secretion with A-particles adhering to their surrounding membrane were extruded into the glandular lumen by reverse pinocytosis. Here A-particles matured into B-particles by budding on the cell membrane. It is likely that there is a direct relation between A- and B-particles because: (1) both particles are always found together in spontaneous mammary tumors in mice, (2) A-particles and the inner part of immature B-particles are morphologically identical; (3) the stereochemical nature of A- and B-particles is similar under the electron microscopy and (4) A-particles are extruded from inside the cytoplasm into the glandular lumen in actively secreting cells.

405. FURTHER CHARACTERIZATION OF INTRACYTOPLASMIC A PARTICLE-ASSOCIATED DNA.

Longfellow DG, Smith GH
Laboratory of Biology, National Cancer Institute, Bethesda, Maryland 20014
J Virol; 17(3):816-823 1976

A DNA species with buoyant densities greater than mouse cellular DNA was found associated with intracytoplasmic A particles (CAP) isolated from mouse mammary tumor virus-infected mouse mammary tumors and mouse Leydig cell tumors which produce CAP but no complete mouse mammary tumor virus virions. This DNA species was absent in identically prepared tissue fractions from tumors which did not contain CAP. Treatment of CAP-associated DNA with pancreatic RNase A did not alter the buoyant density although a reduction in apparent molecular weight (broadening of the DNA band at equilibrium)was observed upon analytical equilibrium sedimentation in CsCl. The molecular weight of untreated CAP-associated DNA was estimated to range from 0.8 10^6 to 3.1 10^6. Base composition analysis showed CAP-DNA to possess an approximate guanine plus cytosine content of 38%. Ninety percent of CAP-associated DNA eluted as single-stranded molecules upon hydroxyapatite column chromatography, a characteristic that accounts in part for its higher buoyant density in neutral CsCl compared to native double-stranded mouse DNA. In two preparations, CAP-DNA had a sedimentation coefficient of 7 to 8S.

406. HIGH-MOLECULAR-WEIGHT DNA ASSOCIATED WITH INTRACYTOPLASMIC A-PARTICLE INCLUSIONS.

Smith GH, Litwack M, Longfellow DG
Natl. Cancer Inst., Bethesda, Md.
Cancer Res; 34(10):2654-2662 1974

Total nucleic acids were isolated from purified intracytoplasmic A particles (purified from transplantable Leydig cell tumors) and analyzed by agarose: acrylamide gel electrophoresis. A major band was observed and found to be DNase sensitive; a minor band migrating in the 4-7S region of the gel was RNase sensitive. Evidence indicated that the DNA was not of cellular origin and not a simple contaminant. Extensive purification of the A particles failed to effect the removal of DNA as a major nucleic acid component and coisolation studies with 3H-thymidine-labeled mouse embryo cells showed that cellular DNA contamination of highly purified A particles was minimal. Analytical equilibrium sedimentation analysis of A-particle-associated DNA and comparison with the buoyant density of tumor cell nuclear DNA isolated from the same tumor pool demonstrated a significantly greater density for A particle DNA. Autoradiographic grain counts obtained from electron micrographs of labeled Leydig cell tumors showed incorporation of 3H-thymidine into A-particle inclusions in situ. These results correlated well with the specific activity of A-particle DNA isolated from these same tumors. The appearance of DNA in close association with purative nucleoprotein cores of mouse mammary tumor virus raises the possibility that this DNA represents the product of the viral reverse transcriptase or, conversely, that A particles are separate entities which share a time and space relationship with mouse mammary tumor virus. These questions must be resolved by molecular hybridization experiments between A-particle DNA and mouse mammary tumor virus 70S RNA.

407. NATURAL ANTIBODY IN MAMMARY TUMOR VIRUS-INFECTED MICE THAT REACTS WITH INTRACYTOPLASMIC A PARTICLES OF MOUSE MAMMARY TUMORS.

Zotter S, Muller M
Institute of Pathology, Medical Academy 'Carl Gustav Carus,' Fetscherstrasse 74, 8019 Dresden, German Democratic Republic
J Natl Cancer Inst; 58(4):967-975 1977

By an indirect immunofluorescence technique with prolonged serum incubation on murine mammary tumor (MT) slices, 179 of 424 mice examined were found to possess natural serum antibody (antibodies) that reacted with intracytoplasmic A particles (iAp) of MT cells. The immunologic specificity of this antibody was supported by absorption and blocking experiments. Furthermore, a strong similarity was seen between the mouse antibody reaction on various MT and the fluorescence pattern of rabbit anti-iAp antiserum on these tumors. In female mice, incidence and geometric mean titers of the antibody in part were correlated to the spontaneous MT frequency of the mouse strains examined. Some mice of the strains XVII/BIn and CBA/BInfXVII/BIn, hitherto regarded as "free" of the mouse mammary tumor virus (MuMTV), also contained anti-iAp antibody in their sera. In contrast to MuMTV-producing CBA/BIn mice, these animals did not possess detectable spontaneous antibody reacting with MuMTV-B particles. Therefore, hypothetically, the antibody response in these mice might be induced by incomplete MuMTV expression. In the

strain CBA/BIn, females 4 months old and older possessed the antibody in significantly higher geometric mean titers when compared to 4-week-old female mice. The history of lactation seemed to have no influence on the titer of antibody. In the comparatively high MT strains CBA/BIn and C3H/BIn, adult (4-month-old) females had the antibody in significantly higher levels when compared to age-matched males. (42 Refs). (Author Abstract)

408. IMMUNOPEROXIDASE STUDIES OF INTRACYTOPLASMIC TYPE A PARTICLES IN MOUSE MAMMARY TUMOR TISSUE CULTURE CELLS (MEETING ABSTRACT).

Hoshino M, Imai M
Lab. Ultrastructural Res., Aichi Cancer Center Res. Inst., Chikusa-ku, Nagoya, Japan
J Electron Microsc (Tokyo); 25(3):180 1976

In order to establish the immunological as well as morphological relationship between intracytoplasmic type A and type B particles, tissue culture cells of C3H/HeJ mouse mammary tumor line were examined by the indirect immunoperoxidase and immunofluorescent methods utilizing a specific antiserum against type A. The antiserum was found specifically to react with the type A particles, the doughnut shaped, inner structure of the budding particles, and the inner structures of the immature and mature type B particles. No type A antigens were detected in the plasma membrane of the budding particles or in the envelope of the type B. It is concluded that the protein moiety of the type A integrates itself into the various stages of particle evolution of mouse mammary tumor virus. (no Refs)

409. AN ELECTRON MICROSCOPIC STUDY OF SPONTANEOUS AND EXPERIMENTALLY INDUCED LEUKEMIA IN ICRC MICE.

Hiraki S, Ranadive KJ, Dmochowski L
M. D. Anderson Hosp. Tumor Inst., Houston, Tex.
Cancer Res; 34(3):474-483 1974

Spontaneous, serially transplanted, and experimentally induced leukemias of ICRC mice were studied by electron microscopy in an attempt to detect the presence of virus particles, if any, and to observe the influence of chemical and hormonal treatment on the presence of these virus particles. The first series of experiments included spontaneous, serially transplanted, and radiation-induced leukemia. The paucity of type C virus particles was quite conspicuous in spontaneous leukemia. Serially transplanted and radiation-accelerated leukemic lesions showed the presence of some type C and intracisternal type A particles. Found in two of these leukemic lesions (thymus and lymphosarcoma), in addition to type C virus particles, were budding and some mature type B virus particles, and numerous intracytoplasmic type A particles. "Viropexis" of type B virus particles has been observed in the lymphosarcoma and in a leukemic thymus gland. The second series of experiments included leukemia induced in ovariectomized ICRC mice with 20-methylcholanthrene (MCA), pituitary transplants, and ovarian hormones (estradiol and estradiol-progesterone). In ovariectomized ICRC mice, leukemic lesions induced by MCA or pituitary transplants, or by MCA and pituitary transplants, showed type C virus particles and, in most cases, intracisternal type A particles. In leukemia induced in ovariectomized ICRC mice by MCA and estradiol, numerous intracytoplasmic type A particles were observed but no type C virus particles. Numerous intracytoplasmic type A particles, as well as budding and some type B virus particles were found in leukemia (thymus and spleen) induced in ovariectomized ICRC mice by MCA (8.0 mg total po dose) and estradiol (1 microg) combined with progesterone (1.0 mg). The large dose of estradiol (10 microg) or a balanced dose of estradiol-progesterone may have stimulated the appearance of numerous intracytoplasmic type A particles, known to be precursors of mammary tumor virus.

XII. REVIEW ARTICLES

A. General Review Articles

410. THE MAMMARY TUMOUR VIRUSES.

Hageman PC
no affiliation given
Int Union Cancer Tech Rep Ser; 20:98-105 1975

The isolation and characterization of mouse mammary tumor viruses (MTV) including descriptions of some analytical techniques, are discussed. Various MTV strains have been isolated from different mouse strains; the exogenous MTV, strains are transmitted by infection, mostly by the mother's milk, while the endogenous MTV strains are genetically transmitted and are usually only slightly oncogenic. The MTV virion is a B particle and contains reverse transcriptase in its core. The major polypeptides are p 28, p 14, and p 10, and the glycoproteins, gp 52 and gp 36. Information for MTV appears to be present in the DNA of all mouse strains investigated. Transcription to RNA occurs in many more tissues than expected, but formation of mature virions is limited to the epithelial cells of the mammary gland and the epididymis. The mouse MTV is the only MTV proven to cause mammary tumors. Indications for the presence of an oncogenic RNA (oncorna) virus are found in human milk and mammary tumors, but the viral etiology of the tumors is not established. MTV can be purified from mouse milk of high mammary-tumor strains and from mammary tumors of these strains but the best starting material is medium from MTV-producing tissue cultures. The method of choice of purification for all oncorna viruses is centrifugation in density gradients. Determination of the infectivity can only be performed in mice of a susceptible strain; titration in vitro in tissue culture is not yet possible. Other detection techniques include electron microscopy, which can establish the presence of mature virions, immunological methods to detect viral antigens, reverse transcriptase tests, and molecular hybridization. Procedures are included for the isolation of B (or C) particles from tumor tissue, extraction of MTV antigens from tissue, preparation of anti-MTV serum in rabbits, absorption of aspecific antibodies from anti-MTV serum, and preparation of micro-Ouchterlony slides.

411. 5TH WALTER HUBERT LECTURE. THE MAMMARY TUMOUR VIRUS (MTV)-A REVIEW.

Muhlbock O
Netherlands Cancer Inst., Amsterdam
Br J Cancer; 28(1):96-101 1973

Demonstration of transmission of mammary carcinoma in certain strains of mice via a factor in the milk of mother mice raised the question of the occurrence of a milk factor in humans. Evidence against this hypothesis were the observations that highest rates of breast cancer are found in human populations of social groups where breast feeding is least practised and that mammary tumor incidence is the same among the paternal as among the maternal grandmothers. Possibly relevant is the discovery of a new Netherlands strain of mice, called GR, in which the tumorigenic factor may be transmitted not only by mother's milk but also via the ovum or the father's sperm. The milk factor has now been shown to be an RNA-virus of unique morphology, called a B-particle. However, based on foster-nursing experiments, mammary tumor viruses (MTV) from different strains of mice differ from one another in biological properties if not in morphology. Another variant of the mouse mammary tumor virus, the nodule inducing virus, is usually present in low concentration, is

transmitted with the genome at conception and has a very low carcinogenic potential. MTV is demonstrable only in a minority of inbred strains of mice. When given to strains of mice which do not naturally harbor the virus, the mammary tumor incidence is usually elevated, but the MTV tends to get lost in the offspring, due to genetic constitution. The finding that BALB/c strain of mice is free of MTV in the first half of its lifespan but shows MTV in its mammary glands later on, and that MTV can be induced in some mouse strains considered MTV-free by treatment with x-rays or urethane, suggests that every mouse may carry genetic information for the production of MTV. Five different MTV-associated antigens have been demonstrated. S1, the principal antigen of the virion, is group-specific. Specific antigens are also found in mammary tumors, but they are very weak, inconstant and difficult to find. Neonatally infected mice are at least partially tolerant to the antigens of the virus and to the virus-associated antigens in infected cells. Attempts to immunize MTV-infected mice against mammary tumors often result in acceleration of tumor growth rather than suppression. Evidence for the occurrence of B-particles in human milk is inconclusive when tested by electron microscopic examination. A so-called simultaneous detection test, applied to milk, yielded wide ranges of positive samples. This test involves detection in milk of 70S single-stranded RNA and of reverse transcriptase, both components of MTV. The positive results could be explained, however, by any of 4 viruses (MTV, type C particles, foamy virus, and Mason-Pfizer virus), all of which may be found in the human population. Other evidence for possible occurrence of B-particles in human milk has been provided by demonstration of poly (A) stretches in 70S from human milk particles, comparable to those found in mouse MTV. Indications of common sequences of nucleotides in RNA viruses of humans and mice was provided by hybridization experiments between mouse MTV/DNA and RNA from human breast tumor tissue. It is concluded, however, that all the experiments have given no definite proof that a complete mammary tumor virus is present in human beings.

412. MAMMARY NEOPLASIA IN MICE.

Nandi S, McGrath CM
Dept. Zool., U. California, Berkeley
Adv Cancer Res; 17:353-414 1973

Past literature relating to the study of spontaneous mammary tumors in mice is summarized briefly, with more recent discoveries being covered in greater detail. Included are sections on inbred mouse strains, neoplastic and preneoplastic lesions, hormonal influences on murine mammary neoplasia, and the susceptibility and resistance to mammary tumorigenesis showed by susceptible and resistant mouse strains. A section on mammary tumor virus (MTV) covers MTV variants, MTV particles, MTV antigens, the detection and distribution of MTV, the effect of MTV and host influences on the virus, the replication and transmission of MTV, the fate of MTV, and the MTV cycle and the role of B particles.

413. MAMMARY TUMOR VIRUS AND HOST GENOME IN THE TRANSMISSION AND CAUSATION OF MAMMARY TUMORS IN MICE.

Heston WE, Parks WP
Lab. Biology, Viral Carcinogenesis Branch, NCI, Bethesda, MD 20014
Can J Genet Cytol; 17(4):493-502 1975

A review of the genetics of mammary tumor viruses is presented. The provirus hypothesis, in theory, brings the mammary cancer problem back into the realm of genetics. The virus is now postulated to be transmitted like a gene. The concept is important in the search for a human breast cancer virus because it more nearly fits existing data on transmission of breast cancer in women when there is no evidence of milk transmission or maternal influence. However, the actual data on which the hypothesis is based do not go much beyond the segregation ratios Bittner had observed in the early 1940's. The occurrence of mammary tumors and their correlation with earlier tests for mouse mammary tumor virus antigen are currently being determined. Mammary tumors have appeared in GR female mice, and there is no reason to suspect that the final incidence will not approach 100%. All tumors observed thus far in the hybrids have been in females that were positive for the mammary tumor virus antigen. Mammary tumors would be expected to appear at a later age if they should occur in negative females. (26 refs)

414. REGULATION OF IMMUNOLOGICAL TUMOR-HOST RELATIONSHIPS IN VIRUS-INDUCED MAMMARY CANCER IN THE MOUSE.

Muller M, Zotter S, Grossmann H, Kemmer C
Carl Gustav Carus Med. Acad., Dresden, Germany
Arch Geschwulstforsch; 42(3):181-191 1973

On the basis of the author's 8 yr of experience and an analysis of the literature, a review is presented about immunological interactions between virus-induced murine mammary carcinomas and hosts infected with mammary tumor virus (MTV). Most of these results were obtained with an MTV-infected strain of CBA/Bln mice. Mice infected perinatally with MTV commonly develop a humoral and cellular immune response to MTV antigens, rather than the complete immunological tolerance that was previously postulated. This basic immunity to MTV may explain in part differences in the behavior of transplanted mammary tumors in MTV-free and MTV-infected mice. The antigenic composition of the tumor cells produces qualitative and quantitative differences in the extent of the immunological reaction of the tumor host. Thus, it is conceivable that the secondary immunological response to viral antigens in the tumor cell is blocked by humoral immunity. The basic immunity may also interfere with immunogenicity of MTV-associated antigens of the tumor cell by "afferent enhancement".

415. INTERNATIONAL CONFERENCE ON RNA VIRUSES AND HOST GENOME IN ONCOGENESIS.

Bentvelzen P
Amsterdam, Holland
Union Int Cancer Bull; 9(2):2 1972

At the International Conference on RNA Viruses and Host Genome in Oncogenesis, held in Amsterdam from May 12-15, 1972, scientists from 19 countries presented their views on how interactions between viruses and host genes may lead to cancer. Several speakers indicated that susceptibility to an oncogenic virus is associated with membrane configuration which in turn might influence virus penetration or the chance for a membrane change leading to neoplasia. With regard to genetic transmission of oncorna viruses, evidence was presented that all mice carry information for a mammary tumor virus. One speaker postulated that a genetically transmitted oncorna virus is switched on during embryogenesis, switched off during normal adult life and switched on during carcinogenesis. Another theory advanced holds that only a partial protovirus is present initially in the germ line; new tumor viruses may originate due to duplication of polymerase, somatic mutation and recombination. Results of a panel discussion suggested that no RNA-instructed DNA polymerase is needed for continuity of germinal proviruses. The enzyme is apparently necessary only for the establishment of a new somatic provirus at a site where no repression of transcription takes place.

416. BIOCHEMICAL CHARACTERIZATION OF MOUSE MAMMARY TUMOR VIRUSES AND RELATED ISOLATES: MASON-PFIZER VIRUS AND THE BUDR-INDUCED GUINEA PIG VIRUS. (PP. 11-56)

Schlom J, Colcher D, Drohan W, Kimball P, Michalides R, Schochetman G

Breast Cancer, Trends in Research and Treatment, A Monograph of the European Organization for Research on Treatment of Cancer. Heuson JC, Mattheiem WH, Rozencweig M, ed. New York, Raven Press Books Ltd, 1976.

The characteristics of mouse mammary tumor viruses (M-MTV) and two related isolates, Mason-Pfizer virus (MPV) and bromodeoxyuridine (BUdR)-induced guinea pig virus (B-GPV), are reviewed and compared. The intracytoplasmic A particle, which may be a precursor of the type B particle, has been observed regularly in cells producing MMTV. Radioimmunoassays have been used to quantitate and characterize variant MMTV's being produced from RIII, GR, DD, BALB/cfC3H, and BALB/c mammary tumor cultures. Virions produced in culture possess the density, sedimentation properties, RNA, and reverse transcriptase activity of MMTV's obtained from mouse milk. Generally, the av primary culture produced approximately 5 X 10^{10} MMTV particles/day/75 cm^2 flask. No common nucleic acid sequences were detected between the RNA's of MMTV's and those of murine leukemia virus (MuLV)-Rauscher, B-GPV, or MPV. The viral genome of the horizontally transmitted variants from GR, RIII, C3H, and A mice was at least 95% homologous, as analyzed by molecular competitive hybridization, and about 25% different from the vertically transmitted variant from C3H-AvyfB mice. The six distinct polypeptides found to be associated with MPV (which was isolated from a rhesus monkey breast carcinoma) may be virus-coded and not derived from host cell components. The similarities of the RNA structure of MPV and B-GPV to that of other oncornaviruses are elucidated. No detectable nucleic acid sequence homology was observed between MPV 60S-70S RNA and the RNA's of types B and C viruses. MPV does not appear to be an endogenous virus of humans. B-GPV is similar to the B-type MMTV in many stages of morphogenesis and appears to be a true endogenous virus. Although there is a lack of detectable sequence homology among B-GPV, MPV, and MMTV, these viruses share several structural and biochemical properties, including a Mg++ cation preference, and they appear to be relatively free of type C particles. (103 Refs)

417. BIOLOGIC CHARACTERISTICS OF TUMOR PROGRESSION IN THE MOUSE MAMMARY GLAND.

Medina D

Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX 77025

Cancer Chemother Rep 2; 5(1):127-131 1975

The murine mammary tumor system is characterized by the presence of a preneoplastic cell population, the hyperplastic alveolar nodule (HAN), which gives rise to mammary tumors. The biologic and tumor-producing characteristics of HAN are reviewed. In the model system, at least two sequential transformations (normal to "nodule" to neoplastic) occur in the process of mammary tumorigenesis. Both chemical and viral carcinogens can act at the level of both normal and nodule populations. Nodules are present in virtually all strains of mice, although their incidence and frequency vary with the status of mammary tumor virus infection, breeding history, and genetic background. Nodule outgrowth lines can be established through the serial transplantation of nodule tissue into the gland-free mammary fat pads of young syngeneic mice and are capable of infinite propagation. These lines still retain a significant degree of responsiveness to local regulatory factors. Most HAN are independent of ovarian and adrenal hormones, but not of anterior pituitary hormones, for growth and tumorigenesis. Exogenously administered prolactin enhances tumorigenic transformation in ovariectomized-adrenalectomized mice. Because of the presence of subpopulations within a HAN, primary nodules can be subdivided to select for differences in growth rate, secretory status, tumor potential, and histogenetic appearance. Three cell populations have been identified: altered epithelia, normal epithelial, and myoepithelial. The epithelial can be divided into ductal and alveolar cells. Removal of the normal component results in restricted growth, suggesting that normal cells exert a significant synergistic effect on the growth of nodule cells. Diets deficient in phenylalanine result in slowed nodule growth. A single dose of cyclophosphamide (20 mg/kg) results in delayed neoplastic transformation. In addition to HAN, ductal hyperplasias are frequent in mice treated with chemical carcinogens, but their preneoplastic nature is still under investigation. It is suggested that the murine mammary tumor system may provide a system with which to investigate the effects of therapeutic drugs not only on growth of established tumors but on transformation from preneoplastic to neoplastic phenotype. (21 refs)

418. THE CELLULAR AND MOLECULAR BIOLOGY OF RNA TUMOR VIRUSES, ESPECIALLY AVIAN LEUKOSIS-SARCOMA VIRUSES, AND THEIR RELATIVES.

Temin HM

McArdle Lab., Univ. Wisconsin, Madison

Adv Cancer Res; 19:47-104 1974

RNA tumor viruses are medium-sized animal viruses with an RNA genome in the virion; virus replication involves a DNA intermediate and the virions contain a DNA polymerase. Rnadnaviruses include avian leukosis-sarcoma virus, mammalian C-type rnadnavirus, viper C-type rnadnavirus, mouse mammary tumor virus, Mason-Pfizer monkey virus, Visna virus, syncytium-forming virus, reticuloendotheliosis virus, and particles related to rnadnaviruses. Virions of all rnadnaviruses are medium-sized, roughly spherical and have a lipid-containing envelope with two external glycoproteins; inside the lipid envelope are 3-5 major proteins, a DNA polymerase, and RNA. Evidence for a DNA intermediate in the replication of Rous sarcoma virus (RSV), and for all RNA tumor viruses and rnadnaviruses as proposed in the provirus hypothesis, is now quite strong. Sequences homologous to much of the RSV genome are present in DNA of RSV-infected cells and sequences homologous to a smaller fraction of the RSV genome are present in the DNA of uninfected chicken cells. It appears most likely that the DNA provirus is synthesized by the virion DNA polymerase with viral RNA as a template and primer; evidence includes the formation of provirus in the presence of cycloheximide, absence of DNA polymerase activity in certain noninfectious RSV and MSV virions, correlation of inactivation of infectivity and DNA polymerase activity after pretreatment of virions with inhibitors, and the existence of two temperature-sensitive RSV mutants with temperature-sensitive DNA polymerase activity. Most neoplasias are not associated with the presence of overt infection by a rnadnavirus. The oncogene hypothesis states that the entire genome of a strongly transforming rnadnavirus is present in all cells and that its activation leads to neoplasia. Hypothesis 3b of Temin suggests that RNA tumor viruses provide only an analogy for most neoplastic transformation; carcinogenesis involves the formation in cells of genes for neoplastic transformation by RNA-directed DNA synthesis.

419. MAMMARY GLAND AS A MORPHOLOGICAL END POINT IN CARCINOGENESIS STUDIES.

Medina D
Baylor Coll. Medicine, Houston, TX 77030
J Toxicol Environ Health; 1(4):551-560 1976

The author describes the induction and characteristics of intermediate preneoplastic mammary cell populations that may be used in a more rapid in vivo assay of carcinogenicity than the appearance of tumors. The hyperplastic alveolar nodule (HAN) is found most frequently and resembles the normal mammary lobules of pregnant mice. HAN's transplanted into syngeneic young female mice evolve into mammary tumors months after transplantation, with the frequency of tumor formation depending on the nodule line used and the mouse strain. Most HAN's are independent of ovarian and adrenal hormones (but not anterior pituitary hormones) for growth and tumorigenesis and are fatpad dependent. The second most frequently encountered lesions are ductal hyperplasias, which appear as atypical proliferations of mammary ducts with abundant intraluminal epithelial proliferations. Histologically, they appear as atypical lesions that exhibit varying degrees of dysplastic growth. Their preneoplastic nature and hormonal dependencies are being investigated. HAN are seen predominantly in mice infected with the mouse mammary tumor virus, while ductal hyperplasias are seen primarily in mice treated with chemical carcinogens. As an in vivo assay, the presence of a biologically active mammary tumor virus can be detected by the induction of HAN nodules in hormone-primed mice within 11-14 wk; tumor development takes 6-8 mo. This assay is not completely reliable for demonstrating the carcinogenicity of a chemical, because mammary tumors may arise in the absence of detectable ductal or alveolar hyperplasias. A similar phenomenon occurs in the chemical carcinogen-treated rat under special conditions, leading to the conclusion that tumor appearance may be more reliable than nodule assay for chemical carcinogens. If the rodent model is applicable to man, potential human mammary carcinogens should be evaluated for both their nodulogenic and tumorigenic potentials under a variety of conditions.

420. ENDOGENOUS MAMMARY TUMOR VIRUSES IN MICE. (PP. 1045-1049)

Bentvelzen P
Radiobiological Institute TNO, Lange Kleiweg 151, Rijswijk, The Netherlands
Tumor Viruses Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor Lab Cold Spring Harbor NY, vol. 39, 1975.

The existence of endogenous mammary tumor viruses (MTV) in mice was studied. In the GR mouse strain, the mammary tumor-inducing agent is transmitted by both the female and male parents. Introduction of the GR strain MTV (MTV-P) into other mouse strains (C3Hf) does not lead to male transmission of the virus, indicating a strong association between the GR genome and MTV-P with regard to gamete-borne transmission. The abnormal mode of MTV-P transmission in the GR strain is controlled by a single dominant Mendelian factor. MTV-L (a virus strain derived from mouse strains from which the milk factor has been removed by foster nursing) is also transmitted at conception by either C3Hf parent, the property apparently being controlled by a single gene located in the same linkage group as the GR gene for MTV-P. EMT6 mammary tumor cells, derived from a BALB/c tumor, were mixed with sperm from various mouse strains; only sperm from the GR strain induced the synthesis of MTV-specific antigens. Genetic transmission was also deduced based on the segregation of MTV-P and MTV-L markers in a test cross of the F1 hybrids between C3Hf and MTV-P. The inducibility of type B oncornaviruses in mouse kidney cells by 5-bromo-2'-deoxyuridine (BUdR) was studied. Exposure to BUdR induced virus in a variety of mouse strains, but it persisted only in C3Hf, DBAf, Gr, and the low-cancer strain BALB/c. The endogenous MTV of BALB/c (MTV-O) was induced in BALB/c by lethal doses of radiation. The data suggest that different genetic systems control the expression of endogenous MTV. Some affect only that germinal provirus with which they are genetically linked, while others have an influence on other germinal proviruses as well as somatic proviruses.

421. ONCOGENIC VIRUSES IN PRIMATES: A REVIEW.

Deinhardt F, Deinhardt JB
Rush-Presbyterian-St. Luke's Med. Cent., Chicago, Ill.
Rush-Presbyt St Lukes Med Bull; 13(2):67-79 1974

The current status of viral oncogeny in primates is reviewed. The basic host-virus interrelationships have been established for several tumors induced in nonhuman primates with C-type RNA and herpes-like DNA viruses. Nonhuman primates are ideal subjects for investigation of the pathogenicity of C-type and MMTV-like viruses, which are endogenous in man and other primates. Antigenic and nucleic acid differences between true oncogenic and endogenous viruses and their similarities to viruses from other species are poorly understood. The oncogenicity of a human virus in primates has been established by HSV- and HVA-induced lymphomas and leukemias and by EBV-induced tumors; such tumor induction supports the suggestion that EBV causes some human neoplasms. Other possible pathogenic mechanisms include C-type RNA virus activation of EBV, EBV activation by C-type RNA virus-transformed cells, and EBV-C-type RNA virus interaction. The recent transformation of cultured primate cells (including human) by HVA may enable transformation of lymphoblastoid cell lines derived from isolated B- or T-cell clones, incidentally providing an important immunologic tool. Viral oncogeny in nonhuman primates has important implications for the study and treatment of human neoplasms.

422. GENETICS OF CANCER.

Heston WE
Natl. Cancer Inst., Bethesda, Md.
J Hered; 65(5):262-272 1974

Studies on the genetics of cancer are reviewed after discussion of the concept that an individual's development is influenced by multiple genes and nongenetic factors. This concept is contrary to an interpretation of single-gene inheritance of cancer. Genetics as related to the etiology and treatment of cancer in man is briefly discussed with emphasis on studies of cancer genetics in animals, particularly the mouse. Studies of tumors resulting from hybridization have shown that tumors can be due to combination of genes affecting tumor development, to introduction of specific genes that increase occurrence of tumors, or to introduction of a tumor virus, specifically the mouse mammary tumor virus, into a more susceptible genetic background. Other studies which are reviewed include those of leukosis in chickens, and cancer-eye in cattle. The genetics of lung tumors and leukemia and the genetic transmission of mammary tumor virus in the mouse are discussed in greatest detail.

423. THE ROLE OF VIRUSES IN MAMMARY CARCINOGENESIS.

Hollmann KH, Verley JM
Lab. Cytopath., Broussais Hosp., Paris, France
Pathol Biol (Paris); 20(1/2):83-103 1972

Mouse mammary tumor viruses (MTV) are described and formation of A and B particles is illustrated. The five major polypeptides of the viruses are enumerated with their

molecular weights, and a comparison is made between proteins and mouse leukemia viruses. MTV antigens and their analysis by immunofluorescence in cell cultures are described. The biological activity cycle of MTV, transmitted from the mother to her offspring by means of her milk, is outlined. The mode of absorption and primary replication in vivo is not known. Not all mice who receive the virus develop a mammary tumor; the oncogenic activity of the virus is conditioned by hormonal, genetic, and immunologic factors in the host. Tests for the detection of MTV are described and include the injection of noncellular extracts into newborn mice; nodulogenesis; the in vitro test of immunodiffusion, and the agglutination inhibition test. Replication of MTV in vitro is also described. Mammary tumors and leukemias are discussed in terms of relationship between B and C particles. Mammary tumors in the rat are described in terms of chemical, hormonal, and viral induction. Mammary tumors in monkeys and in humans are discussed, and the probabilities of a viral origin are argued.

424. IMMUNOLOGY OF MAMMARY GLAND CANCER OF THE MOUSE.

Hollmann KH

Broussais Hosp. Paris, France

Rev Eur Etud Clin Biol; 16(10):969-980 1971

The essential etiologic agent of mouse mammary cancer is mammary tumor virus (MTV), which is usually transmitted through the mother's milk to the nursing young. Tumors then appear at 12-15 months of age and their appearance depends on various factors, especially hormonal ones. The characteristic sudden and simultaneous appearance of several tumors suggests disruption of the equilibrium in the host defense mechanism and points up the importance of immune factors in mouse mammary cancer. The MTV virion, called the "B" particle, is the main antigen for mouse mammary cancer, as has been demonstrated by the immunodiffusion technique in vitro and by the homograft rejection test in vivo. Actually, several antigens are involved, some derived from the envelope and some from the interior of the virion. Tumor-specific antigens, not associated with the virus, have also recently been demonstrated; they vary from one tumor to another, and are not present in all tumors. The immune response of the host against these viral and tumor-specific antigens depends on the integrity of the host's immune system. Particularly important factors in mouse mammary cancer are the age of the mouse at time of infection and the condition of the thymus.

B. Reviews on the Association of MuMTV and Human Cancer

425. SOME ILLUSTRATIVE SYSTEMS OF VIRAL CARCINOGENESIS: MAMMARY TUMOR VIRUS (MTV). (PP. 380-388)

Hageman PC, Muhlbock O

Scientific Foundations of Oncology. Symington T, Carter RL, ed. Chicago, William Heinemann Medical Books Ltd. 1976.

The mouse mammary tumor virus (MTV) and its possible use as a model for human mammary tumors plus investigations using the Bittner virus, the nodule-inducing virus (associated with nodules possessing poor tumor-producing capabilities), GR virus, and several other strains are summarized. Transmission of MTV can occur via milk, egg or sperm, depending on the strain involved. MTV is primarily found in the mammary tumors, mammary glands, and milk of female mice, but it has also been reported in the epididymis, the thymus, in lung tumors, and in a brain tumor. Intracytoplasmic A particles are the probable precursor of the unique, spherical B particle that is the mature virion of the mouse MTV. The electron-dense nucleoid or core can be isolated from virus treated with ether and detergents, sometimes followed by extraction with phospholipase. Several workers have tried to separate polypeptides of the MTV virion - one glycoprotein carries sites antigenically related to the mouse host in addition to MTV-specific antigenic sites. Cross-reactivity between different MTV strains and antigenic differences between the MTV's from C3H, GR, C3Hf, and wild mice have been established in immunodiffusion experiments. In the simultaneous detection test, the RNA and RDDP (RNA-dependent DNA polymerase) of oncornaviruses can be detected simultaneously in milk; however, RNAse is a potent inhibitor in this test. In a search for MTV-specific nucleotide sequences in cellular DNA, no differences were found between the number of MTV-specific DNA copies per cell when GR and C57BL mice were compared. Human embryo cells infected with human milk show viruslike particles containing 70S RNA and RDDP, but the virus has not yet been characterized and the experiments need confirmation. Further studies are necessary to determine whether or not oncornavirus is present in human milk or mammary tumors. (37 refs)

426. MAMMARY TUMOR VIRUS.

Vekaer A

Hopital Universitaire Brugmann, Universite Libre de Bruxelles, Brussels, Belgium

J Gynecol Obstet Biol Reprod (Paris); 4(Suppl2):199-205 1975

Experimental evidence has indicated the presence of a type B oncovirus in the milk of some patients with mammary cancer. This virus has been shown to hybridize with viral RNA from mouse mammary tumor virus (MMTV), which is known to be transmitted through the mother's milk. There is also an antigenic reaction between the serum of some patients with breast tumors and anti-MMTV immunoserum. It is estimated that the milk of 25% of all women contains some viral particles, but the difficulty in getting a clean preparation for examination makes this figure uncertain. However, if this virus could be detected in human milks and breast cancer tissues, it might explain a great deal about human breast cancer.

427. THE MAMMARY TUMOR VIRUSES. (PP. 55-59)

Moore DH

Fundamental Aspects of Neoplasia. Gottlieb AA, Plescia OJ, Bishop DH, ed. New York, Springer-Verlag, 1975.

Studies leading to the detection and partial characterization of a virus in human milk and in breast tumors closely related to the mouse mammary tumor virus (MMTV) are reviewed. Compared with milk from high mammary-tumor strains of mice, human milk contains a relatively low number of virus particles (10^6 and 10^7 particles/ml, respectively). This low concentration coupled with the fact that human milk rapidly destroys the virions is responsible for the poor correlation between the detection of intact RNA virus particles (type B) and the biochemical markers, RNA-directed DNA polymerase and 70S RNA. Evidence that the RNA-directed DNA polymerase and 70S RNA in human milk was associated with type B rather than type C particles came from two different findings: (1) the buoyant density of the particles is the same as that of type B in sucrose gradient centrifugation, and (2) the RNA-directed DNA polymerase from human milk particles is activated by the same cation (Mg^{++}) as type B particles. A number of nucleic acid hybridization experiments have indicated a close relationship between the RNA of MMTV and the RNA found in some human breast cancers. Leukocyte migration inhibition tests have indicated that a large proportion of human in situ tumors contain antigen(s) similar to those of MMTV. Experiments that indicate that some human sera contain antibodies that affect MMTV inc-

TABLE OF CONTENTS

		ABSTRACT NUMBER	
INTRODUCTION			
EDITORIAL COMMENTARY			
I. BIOCHEMICAL STUDIES OF THE MURINE MAMMARY TUMOR VIRUS (MuMTV)			
A. MuMTV Nucleic Acid Studies	1	1-25	1/A8
B. Activities of the MuMTV RNA-Directed DNA Polymerase (RDDP) and Other Enzymes	6	26-46	1/A13
C. Biochemical Studies of MuMTV Structural Components	10	47-67	1/B3
II. GENERAL STUDIES ON THE DETECTION AND CHARACTERIZATION OF MuMTV	15	68-99	1/B8
III. FACTORS INFLUENCING MuMTV EXPRESSION			
A. Hormonal Control of MuMTV Expression In Vitro	22	100-128	1/C1
B. Hormonal Control of MuMTV Expression In Vivo	28	129-150	1/C7
C. Other Factors Affecting MuMTV Expression	33	151-171	1/C12
IV. GENETIC STUDIES OF MuMTV	37	172-183	1/D2
V. IMMUNOLOGICAL STUDIES OF MuMTV			
A. Immunological Assay Procedures	40	184-191	1/D5
B. Immunological Studies of MuMTV Antigenic Determinants	41	192-211	1/D6
C. Autogenous immunity to MuMTV and MuMTV-Induced Tumors	46	212-237	1/D11
D. Alteration of Immunity to MuMTV and MuMTV-Induced Tumors	51	238-264	1/E2
E. Alteration of Immunocompetence by MuMTV	57	265-269	1/E8
F. Tumor Antigens Associated with MuMTV	58	270-281	1/E9
VI. MAMMARY TUMORIGENESIS			
A. Occurrence and Growth of Spontaneous Mammary Tumors	60	282-301	1/E11
B. Growth Control Studies of Transplanted Mammary Tumors	64	302-316	1/F1
VII. STUDIES ON THE ASSOCIATION OF THE MuMTV AND HUMAN CANCER			
A. MuMTV and Human Cancer: Nucleic Acid Studies	67	317-329	1/F4
B. MuMTV and Human Cancer: Enzyme and Protein Studies	70	330-333	1/F7
C. MuMTV and Human Cancer: Immunological Studies	71	334-361	1/F8
VIII. CULTIVATION AND CHARACTERIZATION OF MuMTV INFECTED CELL LINES	77	362-378	1/F14
IX. CELL INFECTIVITY STUDIES OF MuMTV	81	379-393	1/G4
X. MuMTV INTERFERENCE BY OTHER VIRUSES	84	394-397	1/G7
XI. STUDIES OF INTRACYTOPLASMIC A-PARTICLES	84	398-409	1/G7
XII. REVIEW ARTICLES			
A. General Review Articles	87	410-424	1/G10
B. Reviews on the Association of MuMTV and Human Cancer	91	425-462	1/G14
INDEX TO KEY WORDS IN TITLE			
AUTHOR INDEX			

lude neutralization, immunofluorescence of virus-rich mouse mammary tumor tissue, and immunoprecipitation of human serum component(s) on budding MMTV virions. The results of many different experiments indicate that human milk and breast tumors contain a virus closely related to MMTV, but the route of infection and transmission is not known. (18 refs)

428. COMPARATIVE STUDIES ON THE MOLECULAR BASIS FOR A VIRAL INVOLVEMENT IN MURINE AND HUMAN MAMMARY ADENOCARCINOMA. (PP. 311-330)

Michalides R, Feldman S, Spiegelman S, Schlom J
Tumor Virus-Host Cell Interaction; Edited by A. Kolber. (New York: Plenum Press): 1975

Viruslike particles from human and mouse milk have been characterized by isolation of the cores from these particles; the nucleic acid homology between these particles and those from human and murine mammary adenocarcinoma has been confirmed. Mouse mammary tumor virus (MMTV) from RIII mouse milk was treated with phospholipase C ether, the resulting emulsion centrifuged, and the lower aqueous phase layered on a sucrose gradient and recentrifuged. Each fraction was assayed for endogenous DNA polymerase activity in the presence of actinomycin D. The DNA polymerase activity after MMTV core isolation was located in the fraction with a density of 1.23 g/ml. Application of the simultaneous detection test to this fraction gave a clear peak of TCA-precipitable ^{3}H-TTP associated with 70S RNA. Human milk (10-15 samples, each 10-100 ml) was mixed with one-quarter volume of 0.5 M EDTA and centrifuged. The clear milk-plasma zone was recovered and recentrifuged, and the pelleted particles were resuspended and layered over a sucrose gradient. Half of each of the fractions was assayed for the presence of a 70S RNA-associated DNA polymerase; it was seen in the fraction with a density of 1.14-1.20 g/ml. The other half was treated with phospholipase C and subjected to equilibrium centrifugation. 70S RNA particles were found in a fraction with a density of 1.26-1.27 g/ml; no DNA polymerase was found in the viral region of the gradient (density 1.14-1.20 g/ml). If the core preparation from human milk was pretreated with RNase A, no TCA-precipitable ^{3}H-TTP could be found associated with 70S RNA by the simultaneous detection test. This proves that the 70S RNA associated with DNA polymerase in the core particles is a true reverse transcriptase. With the use of ^{3}H-DNA probes, a homology was found in nucleic acid sequences between the virus particles in milk and RNA from mammary adenocarcinomas both in humans and mice. These studies provide evidence of a viral involvement in human breast cancer and a comparable molecular basis for murine and human mammary adenocarcinoma.

429. THE ROLE OF ONCOGENIC VIRUSES IN NEOPLASIA.

Klein PA, Smith RT
Tumor Biology Unit, Dept. Pathology, Univ. Florida Coll. Medicine, Gainesville, FL 32610
Annu Rev Med; 28:311-327 1977

The role of viruses in animal and human cancers is reviewed. Leukemia is transmitted horizontally as a classical infectious disease by oncornaviruses in chickens and domestic cats, and, possibly, in inbred laboratory mice. No compelling epidemiologic evidence exists that either a horizontally or vertically transmitted virus is involved in any human leukemia, but some circumstantial evidence does support such an association. Evidence for the existence of a human analog of the mouse mammary tumor virus (MTV), which causes carcinoma in inbred mice, is found in nucleic acid hybridization experiments and in immunofluorescence tests with mouse mammary tumor cells and sera from breast cancer patients and normal donors. Three groups of DNA-containing viruses, the herpesviruses, adenoviruses, and papovaviruses, have a proved oncogenic potential in animal systems. The herpesviruses have been implicated in the etiology of Burkitt's lymphoma, nasopharyngeal carcinoma, and cervical carcinoma. The adenoviruses have not yet been associated with any type of human cancer. Papovaviruses have been isolated from CNS tissue of patients with progressive multifocal leukoencephalopathy and have been shown to induce brain tumors in newborn hamsters. (117 Refs)

430. RNA TUMOR VIRUSES.

Cardiff RD
Dept. Pathology, Univ. California, Davis, CA 95616
Chemistry; 50(4):12-16 1977

The discovery of reverse transcriptase in RNA tumor viruses has lent major support to the provirus and oncogene theories of carcinogenesis. As predicted by the oncogene theory, mouse leukemia viral DNA has been detected in the cells of all mice tested using radioactive hybridization techniques, including mice in which leukemia is rare. The oncogene theory also predicts that expression of the viral gene is necessary to develop cancer and that animal cells can control virus DNA and keep it from being activated. Certain ordinary body functions may affect cancer growth through proviruses. Hormones that cause female mice to produce milk are also involved in causing breast tumors, and they may be mediated through mouse mammary tumor virus production. Genetic sequences for many tumor viruses have changed very little over millions of years, which may indicate that oncogenes are actually necessary and are kept intact to perform some as yet undetected function. Simply eliminating tumor viruses, therefore, might not be an ideal way to cure cancer. Virus particles have been detected in cells from human leukemia and breast tumor patients in tissue culture, but whether they are tumor virus particles and whether they cause the disease are unknown. (4 Refs)

431. HUMAN CANCER VIRUSES.

Miller G
Yale Univ. Sch. Medicine, New Haven, CT
Adv Intern Med; 21:189-219 1976

The association of viruses with human tumors is discussed with respect to methodological approaches and specific examples of virus-associated tumors. Major methods used to detect viral genomes in tumors include molecular hybridization with nucleic acids and the detection of viral-specified proteins. To establish that a virus is the etiologic agent for a human cancer, one must follow the Koch-Henle postulates: the organism must be readily isolated from patients with the illness; the virus must be isolated in pure state; and experimental disease must be induced with the virus in question. Because of various difficulties involved in determining accordance with any of these postulates, no single category of evidence can be considered sufficient proof that a human virus causes cancer. Other types of evidence that taken together might contribute such proof include: demonstration of the virus in the tumor, recovery of virus from tumors in vitro, cell transformation in vitro, experimental tumorigenesis in animal, seroepidemiologic association, and epidemiologic proofs. The most persuasive evidence for the existence of a human tumor virus comes from studies of the Epstein-Barr virus (EBV), which is intimately associated with infectious mononucleosis, Burkitt's lymphoma (BL), and nasopharyngeal carcinoma (NPC). In general, the data are highly suggestive of an oncogenic role for EBV in both of the latter two. Carcinoma of the cervix appears to be associated with Herpes Simplex Type 2, the biologic properties of which are compatible with properties anticipated for an oncogenic virus. Experiments

attempting to relate an agent similar to the murine mammary tumor virus to human breast cancer have also provided suggestive but incomplete evidence for an etiologic association, and the role of herpesviruses in leukemogenesis in man should be evaluated. At least three different classes of viruses found in man possess biologic attributes of tumor viruses: adenoviruses, cytomegaloviruses, and papovaviruses. Implications of the possible viral etiology of human cancer for prophylaxis are discussed.

432. VIRUSES AND BREAST CANCER. (PP. 45-61)

Moore DH

Tumor Virus Infections and Immunity. Crowell RL, Friedman H, Prier JE, ed. Baltimore, University Park Press, 1976.

The characteristics and posible role of murine mammary tumor viruses (MuMTV) in the development of breast cancer and the existence of a similar virus in human milk and breast tumors are reviewed. The MuMTV's are noninfectious in the strains in which they are endogenous but are highly infectious in mice of certain other strains. When tissues from mouse mammary tumors are adapted to tissue culture, they produce virions in quantities depending on several factors, including the mouse strain from which they are derived. Evidence has been obtained for the horizontal transmission of MuMTV. Mice that receive large quantities of virus in their mother's milk are apparently tolerant to the viral antigens and are not immunized by vaccination. Other mice, however, can be immunized. There is some evidence for the existence in human milk and breast tumors of viruses with properties similar to MuMTV. RNA-directed DNA polymerase (RDDP), a characteristic of RNA tumor viruses, has been found in human milk. Of 29 human breast tumor polysomal RNA preparations used in hybridization experiments, 67% hybridized to a significant extent with labeled MuMTV DNA but not with a Rauscher leukemia DNA probe. Eleven of 36 human breast tissues that have been monitored for MuMTV-related RNA had RNA that hybridized over 10% of the MuMTV probe. These fell into the following classes: 3/6 were in situ, 5/20 invasive carcinomas, and 3/10 nonmalignant breast lesions. There are preliminary suggestions of a correlation between a well-differentiated appearance of tumor cells, a family history of breast cancer, and the presence of MuMTV-related antigens in human breast tissue. (38 refs)

433. 734B: A CANDIDATE HUMAN BREAST CANCER VIRUS. (PP. 63-87)

McGrath CM, Furmanski P, Russo J, McCormick JJ, Rich MA

Tumor Virus Infections and Immunity. Crowell RL, Friedman H, Prier JE, ed. Baltimore, University Park Press, 1976.

An RNA tumor virus-like particle was isolated from the supernatants of cultures of MCF-7 cells, a line established from the pleural effusion of a patient with disseminated malignant adenocarcinoma of the breast. Immunofluorescence studies, using antisera to murine mammary tumor virus (MuMTV) structural antigens, revealed that an antigen was synthesized in MCF-7 cells in association with the synthesis of the RNA tumor virus-like particle (734B). Seven polypeptides of 734B were found to be similar in molecular weight to those of the Mason Pfizer monkey virus (MPMV) grown in human cells and thought to be involved in malignant breast disease in monkeys. Data from immunoprecipitation assays suggest that determinants on the p28 of MuMTV are cross-reactive with determinants on polypeptides of the 734B particle. Hybridization experiments determined that 734B is not identical to various known nonhuman RNA tumor viruses, but MuMTV and 734B appear to be related, with considerable homology between their nucleotide sequences. However, significant mismatching occurs in the hybirds, indicating a significant divergence in the genomes of the two viruses. Two DNA polymerases have been identified in 734B preparations: one functions as a reverse transcriptase in endogenous reactions and the other as a DNA-templated DNA polymerase. Annealing between 734B DNA molecular probes (cDNA's) and cell DNA's occurred only with human and not with nonhuman (including one simian) nuclear DNA. These data suggest an origin for some 734B genes from human DNA. The question of whether 734B was actually generated indigenously from human chromosomal DNA or was inserted into human cell DNA by horizontal transmission followed by genetic divergence can only be resolved by more extensive hybridization studies with 734 cDNA's and a spectrum of cell DNA's selected on the basis of mouse/human phylogeny. (33 refs)

434. RNA TUMOR VIRUSES AND BREAST CANCER.

Schochetman G

Meloy Lab., Springfield, VA

Recent Results Cancer Res; 57:21-25 1976

Recent research on the characteristics and detection of RNA tumor virus in experimental animals and human systems is discussed in relation to human breast cancer. In a study of mouse mammary tumor virus (MMTV), radioactive labeling and gradient centrifugation showed that the radioactive DNA-viral RNA complex sedimented in the 60-70 S region and at the density of RNA. RNA tumor virus-like particles or viral components from human breast tumors have been reported. Reverse transcriptase activity has been obtained from malignant human breast adenocarcinoma. Additionally, molecular hybridization experiments showed that the RNA of human breast cancers contained nucleic acid sequences related to MMTV and to Mason-Pfizer monkey virus. RNA of benign tumors and normal tissues did not hybridize with the viral nucleic acids. Studies of homology between MMTV and resulting mouse tumors transmitted vertically and horizontally indicated that there are two classes of MMTV. The studies discussed indicate that RNA tumor-virus particles or components have been detected in human breast tumors. (19 Refs)

435. EVIDENCE FOR VIRUSES IN HUMAN NEOPLASIAS.

Spiegelman S

Inst. Cancer Res., 99 Fort Washington Ave., New York, NY 10032

Haematologica (Pavia); 60(3):339-372 1975

Several hypotheses explaining the cellular heritability of the cancer state were tested. DNA-RNA hydridizations revealed a pattern of specific RNAs in human tumors showing a remarkable concordance with the predictions deducible from the animal systems. Human breast cancer contained RNA homologous only to that of the murine mammary tumor virus (MMTV). Human leukemias, sarcomas, and lymphomas all contained RNA with sequence homology to the murine leukemia viruses (MuLV). RNA detected in all of the human neoplasias of high molecular weight (1 x 10^7 daltons) and encapsulated with a reverse transcriptase in particles having densities between 1.16 to 1.19 g/ml. Thus, three features diagnostic for the murine oncogenic viruses were satisfied by the particles found in human cancers. Recycling experiments showed that the DNA from human leukemic cells and from lymphomatous tissue contained particle-related sequences that could not be detected in normal DNA. This finding was further substantiated by studies with identical twins that showed that the leukemic twin contained particle-related sequences that could not be detected in the leukocytes of his identical healthy sibling. These results are inconsistent with hypotheses that require chromosomal transmission in the

germ line of complete copies of the information required to produce malignancy and the associated virus particles.

436. VIRUSES AND HUMAN CANCER.

Spiegelman S
No affiliation given
Prog Hematol ; 9:305-330 1975

Experiments to obtain evidence of viral etiology for some human cancer are reviewed. DNA-RNA hybridization was used to determine whether human tumors contain viral-related RNAs. Human breast cancer contained RNA homologous to that of the murine mammary tumor virus (MMTV); human leukemias, sarcomas, and lymphomas all contained RNA with sufficient homology to that of the murine leukemia virus (RLV) to make a stable duplex. The pattern of the unique RNA found in the human neoplasias was in complete agreement with what had been found for the corresponding viral-induced malignancies in the mouse. The simultaneous detection test established that at least a portion of the tumorspecific virus-related RNA detected in human breast cancer and leukemia was a 70S RNA template physically associated with a reverse transcriptase in a particle possessing a density between 1.16-1.19 g/ml, three of the diagnostic features of the animal RNA tumor viruses. The DNA synthesized in the particles from both breast cancer and leukemia hybridized uniquely to the RNA of the corresponding oncornavirus. Recycling hybridization experiments indicated that leukemic cells, and those from Hodgkin's and Burkitt's lymphoma, contain unique sequences not seen in normal cells. In studies conducted with two sets of identical twins, one member of each set having leukemia, a sequence difference was established between the identical twins implying that the additional information found in the DNA of the leukemic member of the set was inserted after zygote formation. This finding argues against the applicability of the virogene hypothesis to this disease, since it demands that the leukemia-specific sequences found in the DNA of the diseased individual must also exist in the genome of his identical twin. The presence of unique sequences in malignant DNA is not consistent with any mechanism for cancer induction that does not involve the insertion of viral-related sequences into the DNA of malignant cells. Further, the identical twin data require the postzygotic insertion into the genome of the viral information, a process known to occur with RNA tumor viruses in animal cells. (44 refs)

437. THE ROLE OF VIRUSES IN CANCER. (PP. 217-251)

Rowson KE
Biology of Cancer. Ambrose EJ, Roe FJ, ed. New York, Halsted Press, 2nd ed., 1975.

The sequence of events in the induction of tumors by viruses is not yet fully understood. In vitro, infected cells undergo a morphological transformation, acquire new properties, and can be shown to be neoplastic upon injection into a suitable recipient animal. In vivo, however, it is more difficult to be sure what occurs. The fate of an individual transformed cell in vivo likely depends on host factors, such as the immune response and the level of circulating hormones, but evidence has been obtained that tumor viruses act directly on the cells whose descendants form a tumor and that such interaction takes place within a few hours of virus injection. Tumor cells produced in vitro and in vivo by the small DNA viruses do not depend on the continuing presence of complete infective virus particles for their neoplastic properties. There is evidence that mammary tumor cells contain a virus with sequences complementary to those in a known mouse mammary tumor virus. The human disease is in some respects similar to that in the mouse, and it appears likely that the production of mammary tumors in the human will involve genetic factors and hormones as well as the virus itself. (258 refs)

438. OF BIRDS AND MICE AND MEN: COMMENTS ON THE USE OF ANIMAL MODELS AND MOLECULAR HYBRIDIZATION IN THE SEARCH FOR HUMAN TUMOR VIRUSES.

Bishop JM, Quintrell N, Medeiros E, Varmus HE
Dept. Microbiol., U. California, San Francisco
Cancer; 34(4):1421-1426 1974

Two paradigms of viral oncogenesis hold that: it is accomplished by the introduction of genetic information into the cell; and that genes homologous to those present in the genomes of laboratory strains of RNA tumor viruses reside in the chromosomes of all normal cells, some of these genes becoming oncogenic when activated. The first is supported by the fact that the infection of either duck or mammalian cells with Rous sarcoma virus (RSV) introduces a new set of genes into the chromosomal DNA of the host cell; this event is a prerequisite for both replication of the virus and neoplastic transformation of the cells. The second paradigm is supported by the fact that virus-induced mammary carcinoma in the mouse can be an inherited disease requiring no genetic information beyond that already present in the mouse genome. Both paradigms subsume the view that RNA tumor virus genes are perpetuated in the host cell as a DNA provirus. Molecular hybridization experiments have shown that, with few exceptions, RNA tumor viruses from different species do not share physically detectable genetic homology. However, the discovery of appreciable homology between the genome of the murine leukemia virus (MuLV) and certain primate C-type viruses indicates that cross-species hybridization may yet prove useful. Although a small amount of hybridization between the murine mammary tumor virus (MMTV) DNA and RNA extracted from human breast carcinomas has been found using relatively nonstringent assay conditions, the nucleotide sequences in the genome of MMTV are too specific to warrant extensive use of murine reagents in the analysis of human breast carcinoma. Molecular studies should be conducted in tandem with biological and genetic analysis of both known and yet-to-be-discovered cancer viruses.

439. PROPERTIES OF THE MOUSE MAMMARY TUMOUR VIRUS AND OF PARTICLES FOUND IN HUMAN MILK. (PP. 377-388)

Moore DH, Sarkar NH, Dion AS, Charney J, Lasfargues EY, Kramarsky B
Host Environment Interactions in the Etiology of Cancer in Man Proceedings of a meeting held at Primosten, Yugoslavia, 27 August-2 September 1972; International Agency for Res. on Cancer (Lyon, France): 1973

Research concerning properties of the murine mammary tumor virus (MuMTV) and particles found in human milk is reviewed. MuMTV virions can be separated in relatively pure form by diluting skimmed mouse milk with buffer and solubilizing the casein with EDTA. Pelletized virus is resuspended and laid over a continuous gradient of Ficoll or sucrose; a large percentage of the virions form a recoverable band. Electron microscopy showed that the virus has a tendency to adhere to other particles and to form aggregates with itself. The pH mobility curve indicated an isoelectric point at pH 2.5; bioactivity showed little falling off between pH 5 and 11. The MuMTV virion has a characteristic membrane with protrusions extending from its outer surface. Viral RNA filaments showed length distribution peaks at 1.2, 2.4, and 3.6 um; the longest molecule had an estimated mol wt of 3.6×10^6 daltons, although sedimentation analysis of extracted RNA indicated a mol wt of 10×10^6 daltons. Treatment of the MuMTV virion with Tween 80 and ether resulted in disruption of the viral membrane and release of the nucleoid, large fragments of membrane, and short pieces of membrane that appeared as rosettes. Screening a variety of neoplasms by im-

munodiffusion and immunofluorescence tests demonstrated MuMTV infection in mammary tumors, ML leukemias, and Leydig cell tumors of MuMTV-infected mice. The following evidence indicates that human breast cancer and the putative virus have some properties in common: in both mouse and man there is a high mammary tumor incidence in particular family groups: particles have been found in human milks that are morphologically similar to MuMTV virions; some human sera have a neutralizing effect on MuMTV; both mouse and human milks contain particle-bound 60S-70S RNA and a resident RNA-templated DNA polymerase; nucleic acid hybridization between mouse virus products and human mammary tumor products has been observed. In addition, in both mouse and man the onset of the tumors occurs at two different periods in life.

440. HUMAN MAMMARY TUMOR VIRUS.
Hollmann KH
Broussais Hosp., Paris, France
Biomedicine; 18(2):103-108 1973

Evidence in support of the existence of a human mammary tumor virus is reviewed. The viral etiology of human breast cancer received initial support in 1971 with the discovery in human milk of B-like (MS) particles resembling murine mammary tumor virus (MTV). Of the three types of MS particles, MS-2 has been found in 30% of all human milks examined, whether or not the milk is from women with a family history of breast cancer. MS-1 and MS-2 particles are present in milk from women in India, the United States and France. In addition, virus-like particles almost identical to MTV have been observed in human breast tissues in four of nine cases of cancer and in two cases of cystic disease. Several lines of evidence suggest that the candidate human breast cancer virus is related to MTV. MTV preincubated with sera from humans with breast cancer is less tumorigenic than control virus following injection into mice. Some human milks contain RNA-dependent DNA polymerase as well as 60-70S RNA. Molecular hybridization studies indicate areas of homology between viral DNA from MTV and cytoplasmic RNA from human breast cancer cells. Finally, the high incidence of breast cancer in some families is consistent with vertical transmission of a human cancer virus.

441. INTERACTION BETWEEN VIRAL AND GENETIC FACTORS IN MURINE MAMMARY CANCER: POSSIBLE IMPLICATIONS FOR HUMAN DISEASE. (PP. 3-9)
Hilgers J, Bentvelzen P
Breast Cancer, Trends in Research and Treatment, A Monograph of the European Organization for Research on Treatment of Cancer. Heuson JC, Mattheiem M, Rozencweig M, ed. New York, Raven Press Books Ltd, 1976.

Results of studies conducted during the past 40-45 yr to investigate the various modes for transmission of murine mammary tumor virus (MTV) are summarized. In the early studies, an extrachromosomal factor was discovered that could be transmitted via the milk, transplacentally, via the male, who transfers the virus to the mother during mating (indirectly), via the male in utero, or via the male postnatally (directly). Besides this extrachromosomal vertical transmission, some evidence exists for horizontal transmission. More recently, chromosomal vertical transmission has been discovered. In GR mice, which have a high incidence of mammary tumors at an early age, the responsible gene may represent a DNA provirus. Molecular hybridization studies show that the normal cellular DNA of all the strains tested so far contains multiple copies of the MTV genome. Host factors may interfere with viral replication and thereby cause resistance to its oncogenic action. A specific gene system controlling viral carcinogenesis is the major histocompatibility locus of the mouse. Although most studies on host resistance have been concerned with an exogenous virus, some resistance factors to endogenous virus have been demonstrated. In humans, viruses transmitted as a genetic factor of the host may contribute to mammary carcinogenesis. (44 Refs)

442. THE GENETIC ASPECTS OF HUMAN CANCER.
Heston WE
Lab. Biology, NCI, NIH, Bethesda, MD 20014
Adv Cancer Res; 23:1-21 1976

The genetic transmission of factors influencing the occurrence of a number of cancers (breast, colorectal, gastric, and lung cancer and retinoblastoma and leukemia) in man is reviewed. There appears to be an inherited influence in the etiology of breast cancer that is especially prominent in premenopausal cancer. Studies suggest that if there is a human breast cancer virus similar to the mammary tumor virus found in mice, it is probably transmitted genetically. From studies of families with more than one case of leukemia, it was concluded that genetic factors had a role in the occurrence of the disease. From information on leukemia viruses in experimental animals, it appears likely that a leukemia virus will eventually be found in man and, if so, it probably also will be genetically transmitted. A number of chromosomal aberrations have been identified that appear to be associated with increased leukemia, but the relationship between the chromosomal aberrations and the leukemia has not been clarified. Genetic factors have also been identified in the adenocarcinoma of the colon arising from inherited polyposis. Multiple polyposis of the colon and Gardner's syndrome (another polyposis important in the genesis of colorectal cancer) are inherited as a single dominant gene, whereas cancer of the large intestine where there is no multiple polyposis is probably polygenic. More gastric cancer has generally been found in relatives of gastric cancer probands than in those of controls, but in some studies the difference has been barely significant. Bilateral retinoblastoma is inherited as a single dominant gene, as is 5%-10% of the more common unilateral cases. Several studies have indicated that inheritance of xeroderma pigmentosum is by a single autosomal recessive gene. The possibility has been suggested that the xeroderma pigmentosum gene increases carcinogenesis by increasing oncogenic virus-induced transformation in cells of patients with the disease. There is a significant increase in lung cancer mortality among the relatives of lung cancer probands that cannot be accounted for by age, sex, generation, or cigarette-smoking factors. The smoking factor appears to be greater than the familial factor among men, but among women the familial factor appears to be greater than the smoking factor. It is concluded that genetic factors may play a role in the etiology of lung cancer together with such environmental factors as cigarette smoking. (88 refs)

443. MOLECULAR VIROLOGY OF CANCER. (PP. 178-197)
Spiegelman S
Molecular Base Of Malignancy, New Clinical and Therapeutic Evidence. Deutsch E, Moser K, Rainer H, Stacher A, ed. Stuttgart, Georg Thieme Publishers, 1976.

DNA-RNA hybridization was used to determine whether human tumors contain viral-related RNA's. The method involved the ability of any piece of single-stranded DNA to find its complementary RNA and form a double-stranded hybrid structure. A survey of human neoplasias with animal virus probes indicated a 67% affinity for breast cancer and a 92% affinity for leukemias. As technology improves, so does the percentage of positive findings. The specificity pattern of the unique RNA found in human neoplasias was in complete agreement with that described for corresponding viral-induced malignancies in mice. The probe generated by particles from

human breast cancer was homologous only to the RNA of mouse mammary tumor virus, whereas the human leukemic probe was related in sequence only to the murine leukemic agent. Unique sequences in Hodgkin's and Burkitt's lymphoma were noted to share sequences with the Rauscher murine leukemia agent. Leukemic twin studies have confirmed a postzygotic insertion of this additional information. Future prospects on this line of research were outlined. (44 refs)

444. MOLECULAR VIROLOGY OF HUMAN NEOPLASIA. (PP. 1-22)

Axel R, Spiegelman S

Oncologic Medicine, Clinical Topics and Practical Management. Sutnick AI, Engstrom PF, ed. Baltimore, University Park Press, 1976.

Molecular evidence for a viral etiology for human cancer was reviewed. By using DNA probes synthesized with the aid of a variety of known RNA animal viruses, it was found that human breast cancer contains RNA homologous only to that of the murine mammary tumor virus. In addition, human leukemias, sarcomas, and lymphomas all contain RNA similar only to that of the murine leukemia virus. The use of a simultaneous detection test permitted further elucidation of these findings. At least a portion of the virus-related RNA that was detected by hybridization was in the form of a 70S RNA template physically associated with a reverse transcriptase, two of the diagnostic features of RNA tumor viruses. Furthermore, the DNA synthesized by human tumor cell reverse transcriptase on its own endogenous template was found to be related in sequence to the analogous murine viral genome. The unique sequences found in the leukemias and lymphomas do not disprove the virogene hypothesis in an absolute sense. In a global biologic context, no collection of individual experiments can eliminate hypotheses that invoke the germ-line transmission of a complete copy of some unspecified viral information required for malignancy and the production of an RNA tumor virus. What is evident in these findings with human leukemias and lymphomas suggests a more optimistic pathway for the control of these diseases. (25 refs)

445. THE MOLECULAR GENETICS OF HUMAN CANCER AND ITS ETIOLOGIC IMPLICATIONS.

Spiegelman S, Axel R, Baxt W, Kufe D, Schlom J

Coll. Physicians and Surgeons, Columbia Univ., New York, N.Y. 10032

Genetics; 79(Suppl):317-338 1975

The genotypic change underlying the cellular transformation to malignancy was studied using the avian myeloblastosis virus (AMV), Rous sarcoma virus (RSV), murine leukemia virus (MuLV), murine sarcoma virus (MuSV), and murine mammary tumor virus (MMTV). DNA-RNA hybridization experiments were performed to determine whether human tumors contain viral-related RNAs. The RNA from human breast cancer cells formed complexes with MMTV viral-specific 3HDNA in 67% of the cases studied, while RLV viral-specific DNA formed complexes with up to 92% of the human leukemia, sarcoma, and lymphoma RNAs. The specificity pattern of the unique RNA found in the human neoplasias was also in complete agreement with what has been described for the corresponding viral-induced malignancies in the mouse. The simultaneous detection test for reverse transcriptase and high molecular weight RNA was used to detect the presence of particles similar to RNA tumor viruses in human material. When this test was applied to human breast cancer, 79% of the malignant samples were positive for the simultaneous detection reaction and all of the control samples from normal and benign tissue were negative. Furthermore, the particles detected by this test localized in sucrose gradients at a density between 1.16 and 1.19 g/ml. the density characterisitic of the oncogenic viruses. When the simultaneous detection test was applied to human leukemias, 22 of the 23 leukemic patients and none of the nonleukemic patients examined showed evidence of specific 70S RNA-directed DNA synthesis. To test the germ-line transmission of viral information (virogene hypothesis), the viral sequences contained in nonneoplastic DNA were removed by exhaustive hybridization with the viral probe to normal DNA in vast excess. The results indicate that the vast majority of normal cells do not contain a particular stretch of malignant information found in the cells of leukemic subjects. The same situation was found when cells from leukemic and nonleukemic identical twins were compared; the leukemic twin contained particle-related sequences which could not be detected in the WBC of the healthy sibling. The data do not support the virogene hypothesis, and are not consistent with the derepression of preexistent malignant sequences. The only etiologic mechanism which is supported is the one that requires the post-zygotic insertion of viral information into the genome.

446. IMMUNOGENICITY AND MUMTV-LIKE ANTIGENICITY OF HUMAN BREAST CANCER TISSUES.

Black MM

New York Medical Coll., Flower and Fifth Ave. Hosps., New York, NY 10029

Contemp Top Immunobiol; 6:239-262 1977

A review of studies on the immunogenicity of breast cancer resulted in the following conclusions: (1) patients vary with regard to the biologically significant immunogenicity of their cancer tissue and the specific hypersensitivity responses to their cancer tissue; (2) prognostically significant immunogenicity and hypersensitivity are maximally present during the preinvasive stage of the disease; and (3) disease progression is associated with or reflects a loss of immunogenicity and/or specific hypersensitivity. In WBC migration tests, positive responses were obtained most regularly when the target was autologous in situ cancer tissue from Stages 0 and I cases. These responses were least common when the target was invasive breast cancer tissue from Stage II breast cancer patients. The response of WBC to autologous invasive breast cancer tissues having similar nuclear grades correlated with the lymphoreticuloendothelial responses. Polyacrylamide gel electrophoresis of the protein components of breast cancer tissue eluates suggests that the antigenic properties of these tissues are correlated with protein components that have antigenic and physicochemical similarities to murine mammary tumor virus (MuMTV) proteins. It appears from the available data that MuMTV-like antigenicity and protein patterns may provide an approach toward the biologically significant characterization of individual cancers. (58 Refs)

447. IMMUNOLOGY: BREAST CANCER.

Heppner GH

Div. Biological and Medical Sciences, Brown Univ., Providence, RI 02908

Recent Results Cancer Res; 57:95-108 1976

The evidence for immune reactivity to human breast cancer is summarized. Antibodies reacting with mouse mammary tumor virus (MTV) have been detected in the sera of some women with breast cancer by several techniques. The migration of WBC from about 30% of breast cancer patients is inhibited by MTV but not by virus-free mouse milk. This WBC reactivity was found in only 5% of patients under 45 yr old, but in 39% of WBC from older patients. Invasive breast carcinomas are less antigenic than in situ disease. Breast cancer patients are generally immunocompetent. (48 Refs)

448. VIRO-IMMUNOLOGY IN BREAST CANCER.
Humphrey LJ
No affiliation given
Breast; 2(4):31-33 1976

Recognition of the role of a virus in the etiology of breast carcinoma goes back several decades to the discovery of the Bittner agent or milk factor. Sufficient data have since demonstrated that the milk factor is a mammary tumor virus. The work of Duran-Reynals on chronic irritation has been applied to the breast. Chronic irritation, with its inflammatory response, occurs in the human breast in a manner that is mechanistically similar to the Duran-Reynals model. However, the existence of a chronic inflammatory response and the implication of a virus similar to murine mammary tumor virus do not constitute proof that human breast cancer is caused wholly or in part by an oncogenic agent. Isolation of the virus from breast cancer tissue and appropriately controlled transformation of normal breast cells to malignant cells would offer convincing evidence. Tumor-associated antigens or antibodies and other immune phenomena have been described, but documentation of breast-cancer-specific antigens and antibodies is still lacking. There is evidence that autoimmune phenomena are associated with breast cancer. Two autoantibodies have been described: one is directed against the Fc of immunoglobulin; the second is an autoantibody directed against the antigen-binding fragment of immunoglobulin. The sera from breast cancer patients and from those with fibroadenoma do react against antigens in breast cancer tissue. (27 Refs)

449. ANTIGENS OF VIRUS-INDUCED MURINE LEUKEMIAS.
Micheel B
No affiliation given
Beitr Krebsforsch; 13:82-156 1974

The literature concerning antigens of virus-induced murine leukemias is reviewed. The identification of revertase in oncornavirus virions supports the concept that the replication of these viruses occurs via the RNA to DNA to RNA pathway. To demonstrate the presence of revertase in humans, the following should be tested: the sensitivity of an endogenous reaction to RNase and a requirement for all four deoxyribonucleoside triphosphates, the specificity in response to certain synthetic templates, and the simultaneous detection of revertase and 70S RNA. It must be determined whether revertase also occurs in normal cells. A DNA polymerase which can use RNA-RNA and RNA-DNA synthetic templates has been detected in a variety of uninfected normal mouse and human cells. There is a positive correlation between the occurrence of type B particles (similar to mouse mammary tumor virus) in the milk of women from breast cancer-burdened families and the presence of revertase. (235 refs)

450. IS THERE EVIDENCE THAT IMMUNITY INFLUENCES TUMOR-HOST BALANCE IN BREAST CANCER?
Heppner GH
Recent Results Cancer Res; 42:63-72 1973

Basic features of mouse mammary tumor immunology are reviewed, including the types of antigens found, the influence of mammary tumor virus infection on the capacity to respond to these antigens, and the types of antitumor immune responses detected by in vitro technics. Correlation between the growth of mammary tumors and the detection of immune responses is discussed, and studies on immune responses to breast cancer in humans are described. The role of immune responses in regulation of the growth of human breast cancer is not resolved, but there are indications that such responses are important. Cellular and humoral responses similar to those detected in mouse mammary tumors can be demonstrated in breast cancer patients. Some of these responses can be correlated with tumor growth in mice; it is likely that the same correlations will be found in humans, and preliminary data are encouraging in this aspect. The therapeutic potential of immune responses in human breast cancer, however, remains to be determined. (45 refs)

451. EPIDEMIOLOGY OF CANCER AND HOST SUSCEPTIBILITY FACTORS: BREAST CANCER. (PP. 49-59)
London WT
Oncologic Medicine Clinical Topics and Practical Management. Sutnick AI, Engstrom PF, ed. Baltimore, University Park Press, 1976.

Several problems associated with epidemiological study of cancer are enumerated: the etiologic agent(s) or class of agents is not known with certainty; cancer is probably the result of an interaction of several factors, each of which must be present; incubation periods are very long; clinical manifestations of pathologically defined cancers are vague or absent; determining whether an association between an agent and cancer is a cause or effect of the disease is difficult; and it is not yet clear what constitutes an adequate control group. Among risk factors related to breast cancer are: ages at first pregnancy, menarche, and menopause; marital status; and androgen and estrogen excretion. Geographic distribution and obesity may reflect a common nutritional factor. The last group consists of familial aggregation, preexisting benign breast disease, and prior occurrence of other cancers. A milk-transmitted viral etiology has not been supported for breast cancer, nor is it clear whether DNA homologous to mouse mammary tumor virus RNA or Mason-Pfizer monkey virus RNA is present in human breast tissue. It is suggested that familial medullary or lobular breast cancer conforms to the Knudson hypothesis, that a cancer gene can be inherited or acquired by mutation. Based on observations of familial and nonfamilial retinoblastoma, the required mutational event may be produced by a virus. Another hypothesis assumes that estrogen secretion in the absence of progesterone results in unopposed estrogenic stimulation and eventually in malignant transformation of the breast ductal epithelium. This endocrine hypothesis may be associated primarily with postmenopausal breast cancer but also with premenopausal cases characterized by infertility, irregular menstration, and anovulatory cycles. It is suggested that here, too, at least one other factor, a virus or chemical carcinogen, is required. (22 refs)

452. EPIDEMIOLOGIC ASPECTS OF MAMMARY TUMOURS.
Cole P
Harvard Sch. Public Health, Boston, Mass.
Proc Int Symp Biol Charact Hum Tumors (Bologna); 1:157-163 1974

The epidemiology of mammary tumors is reviewed with special attention given to those descriptive features related to child-bearing. Two strongly entrenched ideas, that lactation and high parity protect against breast cancer, have been shown to be wrong or noncausal. A new and stronger risk indicator, age at first birth, has emerged, although the association has not been shown to be causal. Age incidence curves suggest breast cancer has a dual etiology or, at least, that there are two periods in a woman's life, possibly adolescence and menopause, when the risk of breast cancer initiation or promotion is relatively high. The major causal hypotheses are reviewed: genetic, viral and endocrine. Although there is an undeniable familial aggregation of breast cancer, the genetic hypothesis suffers since the disease is not transmitted in any recognizable pattern of inheritance. Aggregation is equally

consistent with an environmental exposures. Although B type RNA virus particles similar to the mouse mammary tumor virus have been found in the milk of women with a family history of breast cancer, only a small proportion of the particles seen in human milk are indistinguishable from the mouse virus and the proportion of women excreting such particles is similar among those with and without a family history of breast cancer. While the role of a virus in breast cancer must be evaluated essentially by laboratory techniques, such studies could be enhanced by use of epidemiologic information in the selection of subjects and materials for evaluation. Among the endocrine hypotheses, those concerning estrogens have been strengthened by a comparison of urinary estrogen profiles of women in population with different breast cancer risks.

453. THE ETIOLOGY OF BREAST CANCER. (PP. 15-27)

Rich MA, Furmanski P, McGrath CM, McCormick J, Russo J, Soule H

Steroid Hormone Action and Cancer. Menon KM, Reel JR, ed. New York, Plenum Press, 1976.

The role of viruses in the etiology of breast cancer is explored. There are at least two routes of natural transmission for mouse mammary tumor viruses: by way of the milk and by vertical transmission through viral genomic information integrated into, and transmitted by, the germ cells. A protein has been isolated that is associated with the oncornaviruslike particle in human milk. This protein is present in reverse transcriptase-positive milks and absent in negative milks. Its distribution in density gradients of core preparations coincides with the core-containing bands and their reverse transcriptase activity. The core protein isolated from human milk is electrophoretically identical to the major core protein of mouse mammary tumor virus. MCF-7 cells (from a pleural effusion in a patient with a malignant adenocarcinoma of the breast) synthesize a particle (734B) with all of the characteristics of the known oncornaviruses. The particle, which shares no identity with mammalian leukemia viruses, has a density of 1.17 g/ml and contains a true reverse transcriptase and 70S RNA. Results to date suggest that at least some 734B sequences may be coded by the DNA genome of human cells, but not by nonhuman cells; therefore, 734B may be a human endogenous virus. Final proof that 734B is a human breast cancer virus will require the determination of its specific biological activity. (28 refs)

454. IMMUNOLOGICAL CONTROL OF BREAST CANCER: DISCUSSION.

Stutman O, Herberman RB

Cellular Immunobiology Section, Memorial Sloan-Kettering Cancer Center, New York, NY 10021

Cancer Res; 36(2):781-782 1976

Studies on the response of the immune system to viral mammary tumor antigens in the mouse are analyzed. Although some relationship between tumor-associated antigens and murine mammary tumor (MTV) antigens has been established, further purification of the antigens and cross-reactivity studies are suggested. Of particular interest is the antigenicity of the glycoprotein of MTV. Cell-mediated natural immunity to MTV-associated antigens has been observed in normal mice. The relevance of studies on the mouse mammary tumor to therapy or prophylaxis of human neoplasms is discussed. An immunological association between mouse and human breast cancer has been demonstrated in leukocyte migration inhibition studies and lymphocyte stimulation assays using cells from breast cancer pts and MTV-containing materials. Partially purified skin reactive antigens prepared from human breast cancer reacted with heterologous antisera against MTV or Mason-Pfizer virus in one study; non-virus related material may have caused the cross-reactions observed. Results of studies of mouse mammary tumor systems seem potentially applicable as screening tests for human breast cancer. (13 refs)

455. BIOCHEMICAL EVIDENCE FOR VIRAL INVOLVEMENT IN HUMAN BREAST CANCER. (PP. 61-78)

Schlom J, Colcher D, Michalides R, Schochetman G, Young J, Spiegelman S, Feldman S

Fundamental Aspects of Neoplasia. Gottlieb AA, Plescia OJ, Bishop DH, ed. New York, Springer-Verlag, 1975.

Studies involving the use of DNA probes to detect viral agents in human breast cancer are discussed. Numerous human milk preparations were examined for the presence of virus particles by the simultaneous detection assay. The ^{3}H-DNA complexes generated in an endogenous reaction with human milk particles sedimented in the 60S-70S region and banded at the density of RNA. The 60S-70S RNA of human milk particles contained poly A sequences of the same length as those found in the mouse mammary tumor virus (MMTV), Mason-Pfizer monkey virus (MPMV), and in other known RNA tumor viruses. Cores prepared from MMTV and from human milk particles banded at a density of 1.26 g/ml in sucrose and contained a 60S-70S RNA in association with reverse transcriptase. Using a ^{3}H-labeled DNA probe complementary to the RNA of the human milk particles (cDNA), a homology was shown in nucleic acid sequences between human milk particles and the RNA from human mammary adenocarcinomas. Increased hybridization was observed when human milk cDNA was hybridized to RNA isolated from material banding at 1.15-1.20. The hybridizations between this same ^{3}H-DNA probe and the RNA extracted from analogous fractions of human benign breast tumors, leukemias, or sarcomas were negative. These findings indicate that the ^{3}H-DNA probe detects sequences in the RNA specific for malignant breast tumors. In other experiments, 25% of the MPMV ^{3}H-cDNA synthesized for MPMV 60S-70S RNA hybridized to polysomal RNA from human adenocarcinomas of the breast. The hybrids formed between the MPMV ^{3}H-cDNA probe and the malignant breast tumors were analyzed by equilibrium density centrifugation in Cs2 SO4 and by hydroxylapatite chromatography. Both methods gave positive results in more than two-thirds (27/39) of the breast adenocarcinomas tested, whereas no RNA from 20 human benign breast tumors or normal tissue showed any homology to MPMV. Subviral particulates having the biochemical properties associated with RNA tumor viruses have been isolated using sterox-SL from human malignant breast tumors. It is concluded that these data provide new biochemical evidence to implicate a viral involvement in human breast cancer. (24 refs)

456. BREAST CANCER: ETIOLOGY AND POSSIBLE PREVENTION.

Moore DH, Charney J

Inst. Medical Res., Camden, NJ

Am Sci; 63(2):160-168 1975

Using a mouse as a model, the possible etiological mechanisms of breast cancer are reviewed and applied to human mammary tumor virus. The implications for immunization against breast cancer and the possibility of protection against breast cancer are discussed.

457. EVIDENCE IN FAVOR OF THE EXISTENCE OF HUMAN BREAST CANCER VIRUS.

Moore DH

Inst. Med. Res., Camden, N. J.

Cancer Res; 34(9):2322-2329 1974

Although most human milks destroy or damage the murine mammary tumor virus (MuMTV) and its RNA-

directed DNA polymerase (RDDP), RDDP and type B particles are occasionally found in human milk. RDDP is associated with particles having the same buoyant density as MuMTV and with a 35-70S RNA which is characteristic of RNA tumor viruses. Like MuMTV RDDP, and unlike mouse leukemia virus RDDP, human RDDP responds to magnesium ions for activity with a synthetic template, polyribocytidylic.deoxyguanylic. Hybridization studies indicate a relationship between MuMTV RNA and human breast cancer RNA. Using the migration inhibition factor test, positive responses of human leukocytes to homologous in situ breast cancer tissue are correlated with responsiveness to MuMTV. Many human sera completely neutralize MuMTV. Some human breast cancer sera contain material that precipitates specifically on the membrane of budding MuMTV virions, and slices of mouse tumors rich in MuMTV react in immunofluorescence tests with sera from some women with breast cancer or fibrocystic mastopathy. Thus, some women harbor a virus of apparent similarity to MuMTV. The means of virus transfer in humans is unknown. RNA sequences homologous to MuMTV probes are found in human breast cancers, but to date no homologous DNA sequences have been found. The virus does not seem to be endogenous in humans.

458. VIRUS AND BREAST CANCER.

May-Levin F
No affiliation
Gynecologie; 25(5):487-492 1974

Although the viral origin of a large number of mouse mammary tumors has been known for at least 40 yr, the idea that a virus might play a role in the development of human breast cancer has only been advanced recently. In women, as in animals, the evolution of breast cancer seems related to genetic, geographic and hormonal factors. Epidemiologic, biochemical and immunologic studies seem to point to the presence of a virus in human breast tumors. However, the presence of a virus does not necessarily mean that it is the causative factor. Evidence of type B viral particles similar to mouse mammary tumor virus (MTV) and evidence of reverse transcriptase, indicating the presence of viral RNA, were found in the milk of women with a history of breast cancer.

459. SYMPOSIUM ON BREAST CANCER.

Borden EC, Baker RR, Abeloff MD
Johns Hopkins U. Sch. Med., Baltimore, Md.
Johns Hopkins Med J; 134(2):65-75 1974

Recent evidence suggests that human breast carcinoma is caused by an oncornavirus. Viral-like particles are observed in human milk and oncornavirus markers such as reverse transcriptase, homologous RNA sequences and poly A-rich RNA have been found in human milk and breast cancers. The late development of second primaries in the opposite breast may represent a "reinduction", analogous to that observed in acute leukemia. Immunology studies suggest that breast cancer cells may possess a common antigen to which many breast cancer patients have an IgG antibody. In addition to a common reactivity between patients with breast cancer, cross neutralization between the sera of patients with breast cancer and MMTV have been found. Transmission in man is probably vertical with human milk being a primary factor. The familial nature of human breast cancer was noted as early as 1866. The effects of castration on the growth of established human breast cancer was noted first in 1869. The effects estrogens, pregnancy and oophorectomy on the progression of breast cancer have since been well established. Dietary studies have correlated the intake of sugar and fat with breast cancer incidence. It is suggested that mothers with breast cancer in first-degree maternal relatives or mothers whose husbands have first-degree relatives with a history of breast cancer should not breast feed. Current experimental antiviral chemotherapeutic compounds hold great promise but will not be in general clinical application for another decade. These compounds, interferon, streptovaricin, rifamycins, and polynucleotides, all have a degree of specificity for viral events without effect on normal cell-metabolism, but all are more effective when given prior to the initiation of infection.

460. SEARCH FOR A VIRAL ETIOLOGY OF HUMAN BREAST CANCER.

Lasfargues EV, Moore HD
Inst. Med. Res., Camden, N. J.
J Invest Dermatol; 63(1):125-132 1974

The authors briefly review the steps to the understanding of mouse mammary carcinogenesis and its application to the available human data; the viral hypothesis for breast carcinogenesis in man is discussed. A virus (murine mammary tumor virus, MTV) produced at the cell membrane of mammary epithelial cells can cause mammary tumors in mice. This virus is infective, has spikes on its external membrane, a nucleoid which contains a reverse transcriptase, and a high-molecular-weight RNA. There is no evidence of a similar virus particle budding from the epithelial cells of human breast tumors; however, virus-like structures have been found in human milk and in tissue culture supernatant fractions of human tumor cells. These structures are comparable to the virus-like particles found in the milk of breast cancer patients and are morphologically similar to the murine viruses. Despite the lack of budding viruses in the primary breast tumor cell cultures, biochemical evidence of a reverse transcriptase and a high-molecular-weight (70 S) RNA in these cultures could indicate virus reproduction. Human antibodies from the sera of breast cancer patients will neutralize the antigen localized on the outer membrane of mouse mammary tumor cells. These observations strongly suggest the existence of a human breast cancer virus which has not yet been characterized.

461. BREAST CANCER RESEARCH: PROBLEMS AND PROGRESS.

Marx JL
No affiliation
Science; 184(4142):1162-1165 1974

One of every 15 women will probably develop breast cancer. Efforts are underway to identify those women at greatest risk. The incidence of breast cancer is 5 to 6 times higher in North American and northern Europe than in most of Asia and Africa. Differences in genetic and environmental factors, including diet, are thought to be responsible. Like most other cancers, breast cancer is primarily a disease of old age and appears to run in families. Statistics indicate that breast cancer appears less often in women who have had their first full-term pregnancy before age 30. The female sex hormones are likely involved in the mechanism by which reproductive history influences susceptibility. Both early and late onset of menstruation are associated with an increased risk. Although studies as yet indicate no connection between the disease and oral contraception, these results are viewed with caution as oral contraceptives have been in widespread use for less than 10 years, whereas it takes 15 to 20 years for breast cancer to develop. Hormones of the adrenal and pituitary glands have also been implicated. Many investigators think a virus similar to the mouse mammary tumor virus is involved. A virus with the characteristics of an oncornavirus has been found replicating in a line of cultured cells derived from a patient with carcinoma of the breast. Preliminary evidence indicates the virus may be of human origin. Preventive measures such as the use of drugs to inhibit viral expression or the activity of reverse transcriptase are under investigation. Control of breast cancer currently involves early detection and successful treatment. Detection prior to

metastases is essential. Screening of large numbers of apparently healthy women is a key to controlling the disease and improving the survival rate. Thermography is becoming a useful initial tool in the diagnosis of cancer. Once localized breast cancer is detected, the primary treatment is surgery sometimes accompanied by radiation therapy. Cancers too extensive to remove are treated with radiation or chemotherapy and the removal of one or more of the 3 glands, ovaries, adrenals, or pituitary, known to influence tumor growth. Chemotherapy has recently been used as an adjunct to the primary treatment even though the patient may be clinically free of disease. The presence of carcinoembryonic antigen, methylated guanoxine, or human chorionic gonadotropin in the blood or urine permit identification of patients with a high risk of recurrence.

462. IS BREAST CANCER IN MICE IDENTICAL WITH BREAST CANCER IN WOMEN?

Hollmann MK
Broussais Hosp., Paris, France
Bord Med; 5(6):627-643 1972

The induction of mouse mammary tumors by a virus (MTV) transmitted in the mother's milk is recognized. The virus is an RNA oncornavirus present in all mouse mammary tumors. The particulate matter formed by the virus is called particle B. The manner of elaboration of B particles by cellular tumors appears to be associated with a swelling of surface membranes or with the formation of smaller particles called A particles. These particles are found in the cytoplasm, predominantly in the Golgi area. A tumor cell with intracytoplasmic A particles and B particles situated in the cytoplasmic vacuoles is illustrated. The chemical composition of the mammary tumors includes RNA, lipids, and possibly, polypeptides. Not all mice with this virus develop mammary tumors. Other factors in the development of carcinogenesis include the role of hormones (estrogens); genetic factors which influence hormonal responses and the susceptibility of the gland; and immunologic factors. The mouse tumor possesses an RNA-dependent DNA polymerase called reverse transcriptase. Arguments for a viral origin for human breast cancer are based on the presence of virus-like particles in such cancers and in human milk; the presence of reverse transcriptase in some human milk; the presence of antibodies in human serum which neutralize the mouse tumor virus; the presence of 70S RNA in human milk; and the possibility of hybridization between the RNA from mouse tumors and the RNA extract of human milk; and the possibility of human mammary cancer. Therapeutic measures are delineated.

INDEX TO KEY WORDS IN TITLE

404 IDERATION OF THE MECHANISM INVOLVED IN EXTRUSION OF
350 INE MAMMARY CARCINOMAS: LOCATION OF THE ANTIGEN IN
403 UNG CELLS (SFRE:/ OBSERVATION OF INTRACYTOPLASMIC
52
283 ENESIS IN MICE./
244
243 (PP. 227-244)/
204 NTIGENS, DETERMINED BY IMMUNOPEROXIDASE, IN MAMMARY
324 CE OF VIRAL INVOLVEMENT IN MURINE AND HUMAN MAMMARY
428 FOR A VIRAL INVOLVEMENT IN MURINE AND HUMAN MAMMARY
81 FIVE-YEAR ANALYSIS OF A STRAIN OF MAMMARY
286 OF THERAPY./ SPONTANEOUS MURINE MAMMARY
90 ATYPICAL C PARTICLES IN
45 PROPERTIES OF
190 LEUKOCYTE SUBPOPULATIONS IN THE INDIRECT LEUKOCYTE
315 ABSENCE OF A CO/ CELL DENSITY-DEPENDENT GROWTH IN
300 AMMARY TUMOR VIRUS IN STRAIN GR MICE IN RELATION TO
289 SE MAMMARY TUMOR VIRUS INFECTIVITY AS A FUNCTION OF
216 /BLN MICE INFECTED NEONATALLY WITH T/ SPONTANEOUS
148 STRAINS (S/ TWO-WAY SELECTION OF A STOCK OF SWISS
266 MTV) INFECTION IN MICE: HEMAGGLUTININ RESPONSE AND
128 CYCLIC
304 RY GLAND AS A MARKER OF NEOPLASTIC TRANSFORMATIO/
314 A SOLID TUMOR
438 OF BIRDS AND MICE AND MEN: COMMENTS ON THE USE OF
216 Y WITH T/ SPONTANEOUS AGE-DEPENDENT PRODUCTION OF
337 IC REACTION?./ HUMAN
219 UNOFLUORESCENT DETECTION OF SPONTANEOUSLY OCCURRING
339 ANTIVIRAL AND ANTITUMOR
349 MMARY TUMOR VIRUS. / SPECIFICITY OF HUMAN
217) INFECTION OF CBA/BLN MICE INVOLVING PRODUCTION OF
222 SPONTANEOUS OCCURRENCE OF PRECIPITATING
407 NTRACYTOPLASMIC A PARTICLES OF MOUSE MAM/ NATURAL
338 MOR VIRUS-ASSOCIATED ANT/ IMPLICATIONS OF HUMORAL
227 CELL CYTOXICITY TOWARD THE AUTOLOGOUS TUMOR. /
340 AST CARCINOMA PATIENTS. /
238 IMMUNOTHERAPY OF CANCER WITH
213 ANTIGENS ON THE SURFACES OF GR ASCITES LEUKEMIA /
275 AND A NORMAL ANTIGEN ON THE SU/ DISTRIBUTION AND
197 T OF THERAPY (MEETING/ MOUSE MAMMARY TUMOR VIRUS
341 MPHOCYTE TRANSFORMATION IN VITRO TO RIII MOUSE MILK
259 CED MAMMARY TUMORS AND THEIR LYMPHOCYTE RESPONSE TO
336 HORMONAL STIMULATION OF A VIRUS-RELATED
350 HY WITH MURINE MAMMARY CARCINOMAS: LOCATION OF THE
177 MOR INDUCTION AND EXPRESSION OF MAMMARY TUMOR VIRUS
347 Y TUMOUR VIRUS./ AN
273 EXPRESSION OF THY 1
189 Y RADIOIMMUNOASSAY. / THE PURIFICATION OF A GS
399 (MEET/ LOCALIZATION OF MOUSE MAMMARY TUMOR VIRUS
270 EXPRESSION OF MAMMARY TUMOR VIRUS
275 UTION OF A MAMMARY TUMOR VIRUS-INDUCED AND A NORMAL
394 USES AS DETERMINED BY DO/ LACK OF INTERFERENCE IN
185 MMUNOASSAY FOR MOUSE MAMMARY TUMOR VIRUS-ASSOCIATED
200 IONS BETWEEN MOUSE MAMMARY TUMOR VIRU/ STUDIES ON
192 NE MAMMARY TUMOR VIRUSES./ MULTIPLE
193 H- AND LOW-ONCOGENIC MURINE MAMMAR/ TYPE-SPECIFIC
335 FAVORABLE IMMUNOGENS OF HUMAN BREAST CANCER TISSUE:
196
356 ATHY./ STRUCTURAL,
205 MAMMARY TISSUES OF MICE./
278 AND EMBRYONIC ANTIGENS/ SEARCH FOR CROSS-REACTING
446 IMMUNOGENICITY AND MUMTV-LIKE
279 MAMMARY TUMOR VIRUS-ASSOCIATED
201 F THE MOUSE MAMMARY TUMOR VIRUS: COMPARISON OF THE
215 YTE STIMULATION WITH MAMMARY TUMOR VIRUS ASSOCIATED
272 EXPRESSION OF NORMAL MAMMARY EPITHELIAL CELL

A-PARTICLES FROM THE CELL. / ELECTRON MICROSCOPE STUDIES OF MOUS
A-PARTICLES OF MAMMARY TUMOR VIRUS. / CROSSED REACTION OF HUMAN
A-TYPE PARTICLES IN BABOON C-TYPE PARTICLE INFECTED CHIMPANZEE L
ACTIN IN MAMMARY TUMOR VIRUS (MEETING ABSTRACT).
ACTINOMYCIN D AND X-RADIATION SUPPRESSION OF SPONTANEOUS TUMORIG
ACTIVE SPECIFIC IMMUNOTHERAPY WITH MODIFIED TUMOR CELLS.
ACTIVE SPECIFIC IMMUNOTHERAPY OF CANCER IN EXPERIMENTAL ANIMALS.
ADENOCARCINOMA IN MICE. / LOCALIZATION OF VIRAL A
ADENOCARCINOMA. / EVIDEN
ADENOCARCINOMA. (PP. 311-330) / COMPARATIVE STUDIES ON THE MOLE
ADENOCARCINOMA: MALIGNANCY, STRUCTURE, VIRAL PARTICLES.
ADENOCARCINOMA: MODEL SYSTEM FOR EVALUATION OF COMBINED METHODS
ADENOCARCINOMAS INDUCED BY IMPLANTATION OF FUKU CELLS.
ADENYLATE CYCLASE OF MURINE MAMMARY CARCINOMA.
ADHERENCE INHIBITION ASSAY IN THE MAMMARY TUMOR VIRUS SYSTEM.
AGAR OF BONE MARROW CELLS FROM TUMOR-BEARING BALB/C MICE IN THE
AGE AND TISSUE TYPE. / M
AGE AT INOCULATION, BREEDING, AND TOTAL LAPSED TIME. / MOU
AGE-DEPENDENT PRODUCTION OF ANTIBODIES AGAINST THE VIRION IN CBA
ALBINO MICE FOR MAMMARY TUMORIGENESIS: ESTABLISHMENT OF TWO NEW
ALLOGRAFT SURVIVAL. / IMMUNOLOGIC DEFICIENCY ASSOCIATED WITH MAM
AMP REGULATION OF MAMMARY TUMOR VIRUS PRODUCTION.
ANGIOGENIC CAPACITY OF PRENEOPLASTIC LESIONS OF THE MURINE MAMMA
ANIMAL MODEL PREDICTIVE FOR HUMAN BREAST CANCER.
ANIMAL MODELS AND MOLECULAR HYBRIDIZATION IN THE SEARCH FOR HUMA
ANTIBODIES AGAINST THE VIRION IN CBA/BLN MICE INFECTED NEONATALL
ANTIBODIES BINDING TO THE MOUSE MAMMARY TUMOR VIRUS: A NONSPECIF
ANTIBODIES IN MICE TO INTRACYTOPLASMIC A PARTICLES (IAP) OF MOUS
ANTIBODIES IN MOUSE AND HUMAN BREAST CANCER (MEETING ABSTRACT).
ANTIBODIES TO INTRACYTOPLASMIC TYPE-A PARTICLES OF THE MURINE MA
ANTIBODIES TO MTV. / MAMMARY TUMOR VIRUS (MTV
ANTIBODIES TO THE MAMMARY TUMOR VIRUS IN MICE.
ANTIBODY IN MAMMARY TUMOR VIRUS-INFECTED MICE THAT REACTS WITH I
ANTIBODY IN MICE AND HUMANS TO BREAST TUMOR AND MOUSE MAMMARY TU
ANTIBODY IN THE SERA OF TUMOR-BEARING MICE THAT MEDIATES SPLEEN
ANTIBODY REACTING WITH MOUSE MAMMARY TUMOR VIRUS IN SERUM OF BRE
ANTIBODY.
ANTIBODY-INDUCED MODULATION AND SHEDDING OF MAMMARY TUMOR VIRUS
ANTIBODY-INDUCED REDISTRIBUTION OF A MAMMARY TUMOR VIRUS-INDUCED
ANTIGEN (GP52): A MEANS FOR THE DETECTION OF TUMOR AND ASSESSMEN
ANTIGEN AMONG WOMEN WITH BREAST DISEASE. / LY
ANTIGEN AND MITOGEN. / CORRELATION BETWEEN THE CLINICAL STATUS O
ANTIGEN IN A HUMAN BREAST CARCINOMA CELL LINE, MCF-7.
ANTIGEN IN A-PARTICLES OF MAMMARY TUMOR VIRUS. / CROSSED REACTIO
ANTIGEN IN HORMONE-TREATED OVARIECTOMIZED GR MICE. / GENETIC ANA
ANTIGEN IN HUMAN BREAST CANCER SERA RELATED TO THE MURINE MAMMAR
ANTIGEN IN NORMAL AND NEOPLASTIC MAMMARY CELLS OF MICE.
ANTIGEN OF THE MURINE MAMMARY TUMOR VIRUS AND ITS QUANTITATION B
ANTIGEN ON INTRACYTOPLASMIC A PARTICLE STRUCTURAL POLYPEPTIDES.
ANTIGEN ON THE MEMBRANES OF LYMPHOID CELLS.
ANTIGEN ON THE SURFACE OF MOUSE LEUKEMIA CELLS. / DISTRIBUTION A
ANTIGEN PRODUCTION IN VITRO BETWEEN B-TYPE AND C-TYPE ONCORNAVIR
ANTIGEN. / RADIOI
ANTIGENIC CROSS-REACTIVITY OF ONCOGENIC RNA VIRUSES: CROSS-REACT
ANTIGENIC DETERMINANTS ON THE MAJOR SURFACE GLYCOPROTEIN OF MURI
ANTIGENIC DETERMINANTS ON THE MAJOR EXTERNAL GLYCOPROTEIN OF HIG
ANTIGENIC SIMILARITY TO MURINE MAMMARY TUMOR VIRUS. / PROGNOSTIC
ANTIGENIC STRUCTURE OF MURINE MAMMARY TUMOUR VIRUSES.
ANTIGENIC, AND BIOLOGICAL CHARACTERISTICS OF PRECANCEROUS MASTOP
ANTIGENICALLY DISTINCT FORMS OF MAMMARY TUMOR VIRUS IN BLOOD AND
ANTIGENICITY BETWEEN MAMMARY TUMOR VIRUS-INDUCED MAMMARY TUMORS
ANTIGENICITY OF HUMAN BREAST CANCER TISSUES.
ANTIGENICITY OF L-1210 MURINE LEUKEMIA CELLS.
ANTIGENICITY OF MAMMARY TUMOR VIRUS OBTAINED FROM SEVERAL STRAIN
ANTIGENS IN BALB/C MICE (39179) (MEETING ABSTRACT). / MACROPHAG
ANTIGENS IN MAMMARY NEOPLASIA (MEETING ABSTRACT).

276 RIBUTION OF VIRUS PARTICLES AND MAMMARY TUMOR VIRUS ANTIGENS IN MOUSE MAMMARY TUMORS, TRANSFORMED BALB/C MOUSE KIDNE
191 IN VITRO IMMUNE RESPONSES TO VIRAL AND TUMOR ANTIGENS IN MURINE BREAST CANCER.
195 MAMMARY TUMOR VIRUS (MTV) ANTIGENS IN NORMAL AND MAMMARY TUMOR-BEARING MICE.
358 MASON-PFIZER VIRUS./ COMMON ANTIGENS IN ONCORNAVIRUSES FROM CONTINUOUS HUMAN CELL LINES AND
203 LIN CONSUMPTION TEST WITH MURINE ANTISERA OF COMMON ANTIGENS IN TISSUES INFECTED WITH THE MAMMARY TUMOR VIRUS FROM D
355 NSIDERATIONS OF TUMOR-SPECIFIC AND VIRUS ASSOCIATED ANTIGENS OF HUMAN BREAST CANCERS. / BIOLOGICAL CO
253 THE IMMUNOGENICITY OF VIRAL ASSOCIATED AND PRIVATE ANTIGENS OF MAMMARY CARCINOMAS. / DIFFERENTIAL EFFECT OF NEURAMI
260 LYMPHOCYTE RESPONSE TO MAMMARY TUMOR ANTIGENS OF MAMMARY TUMOR VIRUS IN RELATION TO CLINICAL STATUS.
202 RUS (MULV) IN CELLS OF CULTURES DER/ DETECTION OF ANTIGENS OF THE MOUSE MAMMARY TUMOR (MTV) AND MURINE LEUKEMIA VI
449 ANTIGENS OF VIRUS-INDUCED MURINE LEUKEMIAS.
258 ABSTRACT)./ EFFECT OF SPECIFIC SOLUBLE TUMOR ANTIGENS ON IMMUNE RESPONSES TO MAMMARY TUMORS IN MICE (MEETING
271 MAMMARY TUMOR VIRUS ASSOCIATED ANTIGENS ON THE MEMBRANE OF INFECTED MOUSE SPLEEN CELLS.
213 UCED MODULATION AND SHEDDING OF MAMMARY TUMOR VIRUS ANTIGENS ON THE SURFACES OF GR ASCITES LEUKEMIA CELLS AS COMPARE
210 DOTYPES OF VESICULAR STOMATITIS VIRUS WITH ENVELOPE ANTIGENS PROVIDED BY MURINE MAMMARY TUMOR VIRUS. / PSEU
207 CORRELATION OF IN VITRO AND IN VIVO STUDIES OF ANTIGENS RELEVANT TO THE CONTROL OF MURINE BREAST CANCER.
250 ON NATURAL IMMUNE RESPONSES TO MURINE MAMMARY TUMOR ANTIGENS. / EFFECT OF IMMUNE MANIPULATION
199 AIN SPECIFICITY IN MOUSE MAMMARY TUMOR VIRUS VIRION ANTIGENS. / STR
229 CTIVITY AGAINST TARGET MAMMARY TUMOR CELLS BY VIRAL ANTIGENS. / BLOCKING OF SPLEEN CELL A
194 URINE RNA TUMOR VIRUS (ONCORNAVIRUS) GROUP-SPECIFIC ANTIGENS. / SITES OF SYNTHESIS OF M
218 MPHOCYTE REACTIVITY TO PURIFIED MAMMARY TUMOR VIRUS ANTIGENS. / NATURALLY OCCURRING LY
344 OF REACTIVITY TO VIRAL AND MAMMARY TUMOR ASSOCIATED ANTIGENS. / A FAMILY STUDY
57 OR VIRUS. I. CHARACTERIZATION OF TWO GROUP-SPECIFIC ANTIGENS. / POLYPEPTIDES OF THE MOUSE MAMMARY TUM
213 F GR ASCITES LEUKEMIA CELLS AS COMPARED WITH NORMAL ANTIGENS. / ANTIBODY-INDUCED MODULATION AND SHEDDING OF MAMMARY
48 MOUSE MAMMARY TUMOR VIRUS: II. VIRAL PROTEINS AND ANTIGENS. / CHARACTERISTICS OF THE STRUCTURAL COMPONENTS OF THE
338 EAST TUMOR AND MOUSE MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGENS. / IMPLICATIONS OF HUMORAL ANTIBODY IN MICE AND HUMANS
204 OMA IN MICE./ LOCALIZATION OF VIRAL ANTIGENS, DETERMINED BY IMMUNOPEROXIDASE, IN MAMMARY ADENOCARCIN
278 RY TUMOR VIRUS-INDUCED MAMMARY TUMORS AND EMBRYONIC ANTIGENS: EFFECT OF IMMUNIZATION ON DEVELOPMENT OF SPONTANEOUS
203 IGENS IN TISSUES INFECTED W/ DEMONSTRATION BY THE ANTIGLOBULIN CONSUMPTION TEST WITH MURINE ANTISERA OF COMMON ANT
203 ON BY THE ANTIGLOBULIN CONSUMPTION TEST WITH MURINE ANTISERA OF COMMON ANTIGENS IN TISSUES INFECTED WITH THE MAMMARY
262 OUSE BONE MARROW TRANSPLANTS (MEETING ABSTRACT)/ ANTISERUM-COMPLEMENT TREATMENT OF TUMOR-CONTAMINATED SYNGENEIC M
339 CER (MEETING ABSTRACT)./ ANTIVIRAL AND ANTITUMOR ANTIBODIES IN MOUSE AND HUMAN BREAST CAN
269 ESSION BY SELECTIVE IMMUNOSUPPRESSION WITH CYTOSINE ARABINOSIDE. / CORRECTION OF A MURINE MAMMARY TUMOR VIRUS-ASSOC
213 MAMMARY TUMOR VIRUS ANTIGENS ON THE SURFACES OF GR ASCITES LEUKEMIA CELLS AS COMPARED WITH NORMAL ANTIGENS. / ANTI
276 MORS, TRANSFORMED BALB/C MOUSE KIDNEY CELLS, AND GR ASCITES LEUKEMIA CELLS. / DISTRIBUTION OF VIRUS PARTICLES AND MA
159 MOUSE MAMMARY TUMOR VIRUS IN A MOUSE MAMMARY TUMOR ASCITES LINE (MEETING ABSTRACT). / IN VITRO PRODUCTION OF
254 -SPECIFIC CELL SURFACE COMPONENTS OF HYPOTETRAPLOID ASCITES MAMMARY CARCINOMA CELLS INDUCING HUMORAL REACTIONS IN TH
100 URED CELLS IN THE ABSENCE AND PRESENCE OF HORMONES: ASSAY BY MOLECULAR HYBRIDIZATION. / PRODUCTION OF MOUSE MAMMARY
190 IONS IN THE INDIRECT LEUKOCYTE ADHERENCE INHIBITION ASSAY IN THE MAMMARY TUMOR VIRUS SYSTEM. / THE ROLE OF LEUKOCYTE
230 VITRO DETECTED BY DIFFERENT METHODS OF SERUM FACTOR ASSAY. / SERUM FACTORS IN MAMMARY NEOPLASIA: ENHANCEMENT AND ANT
418 MOLECULAR BIOLOGY OF RNA TUMOR VIRUSES, ESPECIALLY AVIAN LEUKOSIS-SARCOMA VIRUSES, AND THEIR RELATIVES. / THE CELLU
19 RED FOR NEOPLASTIC TRANSFORMATION OF FIBROBLASTS BY AVIAN SARCOMA VIRUSES. / PURIFICATION OF DNA COMPLEMENTARY TO N
388 OR VIRUS IN CAT KIDNEY CELLS INFECTED WITH PURIFIED B PARTICLES FROM RIII MILK. / DETECTION OF MOUSE MAMMARY TUM
56 NSHIP BETWEEN NONGLYCOSYLATED POLYPEPTIDES OF A AND B PARTICLES OF MOUSE MAMMARY TUMOR VIRUS. / PRECURSOR-PRODUCT RE
152 ES IN MOUSE AND HAMSTER KIDNEY CELLS; PRODUCTION OF B- AND C-PARTICLES IN THE MOUSE CELLS. / BIOLOGICAL ACTIVITIES O
394 INTERFERENCE IN ANTIGEN PRODUCTION IN VITRO BETWEEN B-TYPE AND C-TYPE ONCORNAVIRUSES AS DETERMINED BY DOUBLE STAIN I
360 LINES./ B-TYPE ONCORNAVIRUSES ISOLATED FROM CONTINUOUS HUMAN CANCER CELL
32 RACTERIZATION OF RNA-DIRECTED DNA POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS (MEETING ABSTRACT). / ISOLATION AND CHA
33 RACTERIZATION OF RNA-DIRECTED DNA POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS. / ISOLATION AND CHA
3 VISUALIZATION OF THE GENOMIC RNA FROM A B-TYPE TUMOR VIRUS (MEETING ABSTRACT).
147 PRESENCE OF A, B, AND C VIRUS-LIKE PARTICLES IN ORGANS OF RIII/DM/SE MICE.
153 HYBRIDS FROM STRAINS C57BL AND GR: BREEDING TEST OF BACKCROSS SEGREGANTS. / MOUSE MAMMARY TUMOR VIRUS IN
37 DNA SYNTHESIS IN PRENEOPLASTIC NODULE OUTGROWTH OF BALB/C AND C3H MOUSE MAMMARY GLAND. / DNA POLYMERASE ACTIVITY AN
103 C ALVEOLAR NODULES IN VIRGIN AND HORMONE-STIMULATED BALB/C F. C3H AND C3HF MICE. / TUMOR-PRODUCING CAPABILITIES OF H
297 AGENTS ON TUMOR-PRODUCING CAPABILITIES OF SERIES D BALB/C MAMMARY NODULE OUTGROWTH LINES. / EFFECTS OF VARIOUS ONCO
130 C3H AND (C3HF/ APPEARANCE OF VIRUS PARTICLES IN BALB/C MAMMARY NODULE OUTGROWTH LINES TRANSPLANTED INTO BALB/CF.
215 ION WITH MAMMARY TUMOR VIRUS ASSOCIATED ANTIGENS IN BALB/C MICE (39179) (MEETING ABSTRACT). / MACROPHAGE MIGRATION
281 OF PRENEOPLASTIC AND NEOPLASTIC MAMMARY TISSUES OF BALB/C MICE FREE OF THE MAMMARY TUMOR VIRUS. / STUDIES ON THE IM
374 TIC MAMMARY NODULE OUTGROWTH IN MAMMARY FAT PADS OF BALB/C MICE IN ORGAN CULTURE. / PROLIFERATION OF PRENEOPLAS
315 WTH IN AGAR OF BONE MARROW CELLS FROM TUMOR-BEARING BALB/C MICE IN THE ABSENCE OF A COLONY-STIMULATING FACTOR. / CEL
46 OMAL N-ACETYL-GLUCOSAMINYL-TRANSFERASES ACTIVITY IN BALB/C MICE INFECTED WITH MOUSE MAMMARY TUMOR VIRUS (M-MTV).
298 MARY TUMORS FROM PRENEOPLASTIC NODULE OUTGROWTHS IN BALB/C MICE. / CARCINOGEN-INDUCED MAM
282 E OF SPONTANEOUS MAMMARY CARCINOMATA IN A COLONY OF BALB/C MICE. / UNUSUALLY HIGH INCIDENC
36 OPLASTIC NODULES AND TUMORS OF THE MAMMARY GLAND OF BALB/C MICE. / RNA-DEPENDENT DNA POLYMERASE IN PRENE
312 MMARY TUMOR GROWTH AND PITUITARY PROLACTIN LEVEL IN BALB/C MICE. / EFFECT OF ERGOCORNINE ON TRANSPLANTED MA
141 C3H AND RIII MAMMARY TUMOR VIRUSES IN VIRGIN FEMALE BALB/C MICE: BRIEF COMMUNICATION. / BIOACTIVITY OF
14 -INDUCED" MALIGNANT MAMMARY EPITHELIAL CELLS OF THE BALB/C MOUSE (MEETING ABSTRACT). / LEVELS OF MMTV SEQUENCES IN
276 VIRUS ANTIGENS IN MOUSE MAMMARY TUMORS, TRANSFORMED BALB/C MOUSE KIDNEY CELLS, AND GR ASCITES LEUKEMIA CELLS. / DIST
130 H LINES TRANSPLANTED INTO BALB/CF. C3H AND (C3HF X BALB/C)F1 MICE. / APPEARANCE OF VIRUS PARTICLES IN BALB/C MAMMAR
130 /C MAMMARY NODULE OUTGROWTH LINES TRANSPLANTED INTO BALB/CF. C3H AND (C3HF X BALB/C)F1 MICE. / APPEARANCE OF VIRUS
396 ON AND EXPRESSION OF THE LEUKEMIA INDUCING AGENT IN BALB/CF(RIII) MICE. / TRANSMISSI
367 CULTIVATION AND CHARACTERIZATION OF BALB/CFC3H MAMMARY TUMOR CELL LINES.
395 ON OF MAMMARY TUMOR VIRUS AND LEUKEMIA VIRUS IN THE BALB/CFRIII MOUSE. / PRESENCE AND TRANSMISSI
178 TRAIN./ BALB/CFRIII: A NEW HIGH MAMMARY-TUMOR AND HIGH LEUKEMIA MOUSE S
70 MIC CELL-ASSOCIATED MAMMARY TUMOR VIRUS ACTIVITY IN BALB/CF3H MICE. / HE
242 PRETREATED WITH THE METHANOL EXTRACTION RESIDUE OF BCG AND PREVENTION OF ACCELERATION BY CONCOMITANT SPECIFIC IMMUN
247 INOMAS USING DIRECT INJECTIONS OF NEURAMINIDASE AND BCG. / REGRESSION OF SPONTANEOUS MAMMARY CARC
240 H THE METHANOL-EXTRACTION RESIDUE (MER) FRACTION OF BCG: SOLID TUMORS. / IMMUNOTHERAPEUTIC STUDIES IN MICE WIT
252 EXTRACTS IN VITRO/ DIFFERENTIAL RESPONSE OF TUMOR BEARER AND NORMAL MOUSE SPLEEN CELLS TO PHA AND SYNGENEIC TUMOR

71 VIRUS./
141 LE BALB/C MICE: BRIEF COMMUNICATION./
136 ANTITATIVE CONSIDERATIONS./ NODULE
72 GENOUS MURINE MAMMARY TUMOUR VIRUS AS DETERMINED BY
182 INHERITANCE OF SUSCEPTIBILITY TO ERYTHROCYTE-BORN
378 IA C PARTICLES FROM MURINE CELL LINES INFECTED WITH
267 N (MEETING ABSTRACT). / ENHANCEMENT OF
229 LLS BY VIRAL ANTIGENS./
285 IGENICALLY DISTINCT FORMS OF MAMMARY TUMOR VIRUS IN
168 ION ON MAMMARY TUMOR VIRUS ACTIVITY ASSOCIATED WITH
18 ITY OF A DNA-CONTAINING MAMMARY TUMOUR VIRUS IN RED
71 BIOACTIVITY AND VIRIONS IN THE
315 OF A CO/ CELL DENSITY-DEPENDENT GROWTH IN AGAR OF
262 ENT TREATMENT OF TUMOR-CONTAMINATED SYNGENEIC MOUSE
150 COMAS INDUCED BY 226RA: A STUDY OF THE INDUCTION OF
50 ABELING OF MUMTV WITH A GALACTOSE OXIDASE-TRITIATED
99 MAMMARY-TUMOR VIRUS ACTIVITY IN
332 LAR WEIGHT AND RNA-DIRECTED DNA POLYMERASE IN HUMAN
339 TIVIRAL AND ANTITUMOR ANTIBODIES IN MOUSE AND HUMAN
357 LOGIC FEATURES (MEETING ABSTRACT)./ FULMINATING
350 CINOMAS: LOCATION OF / CROSSED REACTION OF HUMAN
462 IS
462 IS BREAST CANCER IN MICE IDENTICAL WITH
320 A./ PRESENCE IN HUMAN
80 IGATIONS ON MAMMARY TUMOR VIRUS DETECTION IN MURINE
331 AND CHARACTERIZATION OF THE DNA POLYMERASE OF HUMAN
351 ONCORNAVIRUS MARKERS ON PERIPHERAL LYMPHOCYTES OF
461
347 AN ANTIGEN IN HUMAN
335 OR / PROGNOSTICALLY FAVORABLE IMMUNOGENS OF HUMAN
446 IMMUNOGENICITY AND MUMTV-LIKE ANTIGENICITY OF UMAN
457 EVIDENCE IN FAVOR OF THE EXISTENCE OF ..UMAN
433 734B: A CANDIDATE HUMAN
352 (MEETING/ LEUKOCYTE MIGRATION INHIBITION IN HUMAN
434 RNA TUMOR VIRUSES AND
448 VIRO-IMMUNOLOGY IN
447 IMMUNOLOGY:
459 SYMPOSIUM ON
458 VIRUS AND
345 INHIBITION BY MAMMARY TUMOR VIRUS IN PATIENTS WITH
348 OF MURINE MAMMARY TUMOR VIRUS BY SERA OF WOMEN WITH
460 SEARCH FOR A VIRAL ETIOLOGY OF HUMAN
191 UNE RESPONSES TO VIRAL AND TUMOR ANTIGENS IN MURINE
314 A SOLID TUMOR ANIMAL MODEL PREDICTIVE FOR HUMAN
207 UDIES OF ANTIGENS RELEVANT TO THE CONTROL OF MURINE
453 THE ETIOLOGY OF
432 VIRUSES AND
451 EMIOLOGY OF CANCER AND HOST SUSCEPTIBILITY FACTORS:
455 BIOCHEMICAL EVIDENCE FOR VIRAL INVOLVEMENT IN HUMAN
9 SIS OF MURINE MAMMARY CARCINOMA: A MODEL FOR HUMAN
450 ENCE THAT IMMUNITY INFLUENCES TUMOR-HOST BALANCE IN
454 IMMUNOLOGICAL CONTROL OF
456
330 MURINE TUMOR VIRUS-LIKE PROTEINS IN HUMAN
333 UCTED DNA POLYMERASE AND VIRUS-RELATED RNA IN HUMAN
392 F CANCER: PENETRATION OF MATURE VIRUS PARTICLES OF
355 MOR-SPECIFIC AND VIRUS ASSOCIATED ANTIGENS OF HUMAN
319 REPLICATION OF ONCORNAVIRUS-LIKE PARTICLE IN HUMAN
336 L STIMULATION OF A VIRUS-RELATED ANTIGEN IN A HUMAN
334 MUMTV-LIKE CHARACTERISTICS OF HUMAN
340 REACTING WITH MOUSE MAMMARY TUMOR VIRUS IN SERUM OF
341 N VITRO TO RIII MOUSE MILK ANTIGEN AMONG WOMEN WITH
343 EFFECT OF MURINE MILK SAMPLES AND HUMAN
338 LICATIONS OF HUMORAL ANTIBODY IN MICE AND HUMANS TO
140 THE ROLE OF PHYSIOLOGICAL STRESS ON
318 HOMOLOGY BETWEEN HUMAN
236 TOMY ON MAMMARY TUMORIGENESIS./ MOUSE STRAIN AND
153 Y TUMOR VIRUS IN HYBRIDS FROM STRAINS C57BL AND GR
289 US INFECTIVITY AS A FUNCTION OF AGE AT INOCULATION,
387 EXPERIMENTAL INFECTION OF A
388 LK./ DETECTION OF MOUSE MAMMARY TUMOR VIRUS IN
123 METHASONE ON THE MOUSE MAMMARY TUMOR VIRUS GROWN IN
40 BY RNA TUMOR VIRUSES AND HUMAN MILK PARTICULATE/
41 A POLYMERASE ACTIVITY IN FIVE RNA VIRUSES: DIVALENT
216 DENT PRODUCTION OF ANTIBODIES AGAINST THE VIRION IN
217 MAMMARY TUMOR VIRUS (MTV) INFECTION OF
280 SCOPY OF VIRUS-INDUCED MAMMARY TUMORS IN MOUSE LINE
80 R VIRUS DETECTION IN MURINE BREAST CANCER OF STRAIN

BIOACTIVITY AND VIRIONS IN THE BLOOD OF MICE WITH MAMMARY TUMOR
BIOACTIVITY OF C3H AND RIII MAMMARY TUMOR VIRUSES IN VIRGIN FEMA
BIOASSAY OF THE MOUSE MAMMARY TUMOR VIRUS: MODIFICATIONS AND QU
BIOASSAY. / ORGAN DISTRIBUTION OF EXO
BITTNER VIRUS IN MICE.
BITTNER VIRUS-CONTAINING INOCULA. / RELEASE OF LEUKEM
BLOCKING FACTOR PRODUCTION BY MAMMARY TUMOR VIRUS (MTV) INFECTIO
BLOCKING OF SPLEEN CELL ACTIVITY AGAINST TARGET MAMMARY TUMOR CE
BLOOD AND MAMMARY TISSUES OF MICE. / ANT
BLOOD CELLS AND MAMMARY TUMOR CELLS. / DIFFERENTIAL EFFECT OF IO
BLOOD CELLS OF MOUSE. / POSSIBIL
BLOOD OF MICE WITH MAMMARY TUMOR VIRUS.
BONE MARROW CELLS FROM TUMOR-BEARING BALB/C MICE IN THE ABSENCE
BONE MARROW TRANSPLANTS (MEETING ABSTRACT). / ANTISERUM-COMPLEM
BONE TUMOURS IN MICE. / VIRUSES IN OSTEOSAR
BOROHYDRIDE METHOD. / EXTRINSIC L
BRAIN AND LIVER OF GR STRAIN MICE.
BRAIN TUMORS (MEETING ABSTRACT). / PARTICLES WITH RNA OF HIGH M
BREAST CANCER (MEETING ABSTRACT). / AN
BREAST CANCER (POUSSE EVOLUTIVE) IN TUNISIA: CLINICAL AND IMMUNO
BREAST CANCER AND FIBROCYSTIC MASTOPATHY WITH MURINE MAMMARY CAR
BREAST CANCER IN MICE IDENTICAL WITH BREAST CANCER IN WOMEN?
BREAST CANCER IN WOMEN?
BREAST CANCER OF RNA HOMOLOGOUS TO MOUSE MAMMARY TUMOUR VIRUS RN
BREAST CANCER OF STRAIN CBA/B1N. / COMPARATIVE INVEST
BREAST CANCER PARTICLES. / PURIFICATION
BREAST CANCER PATIENTS. (MEETING ABSTRACT).
BREAST CANCER RESEARCH: PROBLEMS AND PROGRESS.
BREAST CANCER SERA RELATED TO THE MURINE MAMMARY TUMOUR VIRUS.
BREAST CANCER TISSUE: ANTIGENIC SIMILARITY TO MURINE MAMMARY TUM
BREAST CANCER TISSUES. /
BREAST CANCER VIRUS.
BREAST CANCER VIRUS. (PP. 63-87)
BREAST CANCER WITH MOUSE MAMMARY TUMOR VIRUS, GP-52 AND GP-70.
BREAST CANCER.
BREAST CANCER.
BREAST CANCER.
BREAST CANCER.
BREAST CANCER.
BREAST CANCER. / LYMPHOCYTE
BREAST CANCER. / NEUTRALIZATION
BREAST CANCER.
BREAST CANCER. / IN VITRO IMM
BREAST CANCER.
BREAST CANCER. / CORRELATION OF IN VITRO AND IN VIVO ST
BREAST CANCER. (PP. 15-27)
BREAST CANCER. (PP. 45-61)
BREAST CANCER. (PP. 49-59) / EPID
BREAST CANCER. (PP. 61-78) /
BREAST CANCER. / A COMPARATIVE STUDY OF THE BIOLOGIC AND MOLECUL
BREAST CANCER? / IS THERE EVID
BREAST CANCER: DISCUSSION.
BREAST CANCER: ETIOLOGY AND POSSIBLE PREVENTION.
BREAST CANCERS (MEETING ABSTRACT).
BREAST CANCERS (MEETING ABSTRACT). / PARTICLES CONTAINING RNA-I
BREAST CANCERS INTO VIRUS-PRODUCING CELLS IN VIVO. / THE VIROLOG
BREAST CANCERS. / BIOLOGICAL CONSIDERATIONS OF TU
BREAST CARCINOMA CELL LINE, MCF-7.
BREAST CARCINOMA CELL LINE, MCF-7. / HORMONA
BREAST CARCINOMA IMMUNOGENS.
BREAST CARCINOMA PATIENTS. / ANTIBODY
BREAST DISEASE. / LYMPHOCYTE TRANSFORMATION I
BREAST TISSUE ON HUMAN LEUKOCYTE MIGRATION INDICES.
BREAST TUMOR AND MOUSE MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGENS.
BREAST TUMOR INCIDENCE IN MICE.
BREAST TUMOUR RNA AND MOUSE MAMMARY TUMOUR VIRUS GENOME.
BREEDING STIMULATION AS FACTORS INFLUENCING THE EFFECT OF THYMEC
BREEDING TEST OF BACKCROSS SEGREGANTS. / MOUSE MAMMAR
BREEDING, AND TOTAL LAPSED TIME. / MOUSE MAMMARY TUMOR VIR
CAT KIDNEY CELL LINE WITH THE MOUSE MAMMARY TUMOR VIRUS.
CAT KIDNEY CELLS INFECTED WITH PURIFIED B PARTICLES FROM RIII MI
CAT KIDNEY CELLS. / EFFECT OF DEXA
CATION PREFERENCES FOR POLY(RC).OLIGO(DG)-DIRECTED DNA SYNTHESIS
CATION REQUIREMENTS (MEETING ABSTRACT). / RNA-DEPENDENT DN
CBA/BLN MICE INFECTED NEONATALLY WITH THE MAMMARY TUMOUR VIRUS (
CBA/BLN MICE INVOLVING PRODUCTION OF ANTIBODIES TO MTV.
CBA/BLN. / IMMUNOFLUORESCENCE AND IMMUNOELECTRON MICRO
CBA/B1N. / COMPARATIVE INVESTIGATIONS ON MAMMARY TUMO

116 MMARY TUMOR VIRUS./
106 ENCY VARIATION IN MAMMARY TUMOR VIRUS EXPRESSION IN
151 ENCY VARIATION IN MAMMARY TUMOR VIRUS EXPRESSION IN
365 N OF MOUSE MAMMARY TUMOR VIRUSES FROM PRIMARY TUMOR
372 LY EXPANDING AND COLLAPSING SECRETORY STRUCTURES IN
161 TRANSFORMATION OF X/GF MOUSE EMBRYO
125 REATED, 5-IODODEOXYURIDINE-STIMULATED MAMMARY TUMOR
366 N OF MOUSE MAMMARY TUMOR VIRUSES FROM PRIMARY TUMOR
369 ION./ REPLICATION OF MAMMARY TUMOR VIRUS IN TUMOR
227 THE SERA OF TUMOR-BEARING MICE THAT MEDIATES SPLEEN
315 TUMOR-BEARING BALB/C MICE IN THE ABSENCE OF A CO/
257 E MECHANISMS AGAINST MAMMARY TUMORS BY INCOMPLETE T
156 UNOFLUORESCENCE STUDY (MEETING ABSTR/ EFFECTS OF
118 IMULATED ONCORNAVIRUS-PRODUCING MOUSE MAMMARY TUMOR
387 EXPERIMENTAL INFECTION OF A CAT KIDNEY
359 AN ONCORNAVIRUS ISOLATED FROM HUMAN CANCER
346 UDY OF AN ONCORNAVIRUS ISOLATED FROM A HUMAN CANCER
152 ARY TUMOR VIRUS PRODUCTION IN A MOUSE MAMMARY TUMOR
368 ETING AB/ AN ESTABLISHED RIII MOUSE MAMMARY TUMOR
254 ITES MAMMARY CARCINOMA CELLS INDUCING HUMORAL RE/
83 ODUCTION OF AN ONCORNAVIRUS BY THE CONTINUOUS HUMAN
319 NCORNAVIRUS-LIKE PARTICLE IN HUMAN BREAST CARCINOMA
336 A VIRUS-RELATED ANTIGEN IN A HUMAN BREAST CARCINOMA
362 CULTURE. 1. ESTABLISHMENT OF A MOUSE MAMMARY TUMOR
363 TRANSPLANTABILITY OF CONTINUOUS MOUSE MAMMARY TUMOR
358 ON ANTIGENS IN ONCORNAVIRUSES FROM CONTINUOUS HUMAN
376 M-FREE MEDIUM/ PROPAGATION OF MOUSE MAMMARY TUMOR
68 ON OF THE VIRIONS IN THE IN VITRO L1210(V) LEUKEMIA
378 RELEASE OF LEUKEMIA C PARTICLES FROM MURINE
367 ON AND CHARACTERIZATION OF BALB/CFC3H MAMMARY TUMOR
360 NCORNAVIRUSES ISOLATED FROM CONTINUOUS HUMAN CANCER
231 S TO MTV-INDUCED MAMMARY TUMORS. ACTIVITY · SPLEEN
313 CT). /
254 OMA CELLS INDUCING HUMORAL RE/ CELL LINE-SPECIFIC
255 HUMORAL REACTIONS IN SYNGENEIC HOSTS AGAINST TUMOR
53 OPE GLYCOPROTEIN (GP52) ON MOUSE MAMMARY EPITHELIAL
261 ROLE OF H-2 HISTOCOMPATIBILITY ON GENERATION OF
354 SCUSSION. / SPECIFICITY OF
214 IMARY MAMMARY TUMOURS./
237 THE ROLE OF T AND SUPPRESSOR CELLS IN MTV-DIRECTED
369 TUMOR CELL CULTURES: DEPENDENCE OF HORMONE-INDUCED
162 PROTEINS FOR AN RNA TUMO/ INDEPENDENT POLYPEPTIDE
327 R EVIDENCE FOR VIRAL AGENTS IN HUMAN CANCER AND ITS
284 POSITIVE CORRELATION OF
370 O: COMPARISON OF SATURATION DENSITY, MORPHOLOGY AND
206 BINDING OF
242 ON RESIDUE OF BCG AND PREVENTION OF ACCELERATION BY
360 B-TYPE ONCORNAVIRUSES ISOLATED FROM
83 PRODUCTION OF AN ONCORNAVIRUS BY THE
358 COMMON ANTIGENS IN ONCORNAVIRUSES FROM
363 GROWTH PROPERTIES IN VITRO AND TRANSPLANTABILITY OF
88 TUMOR VIRUS: ISOLATION AND CHARACTERIZATION OF THE
323 OR ONCORNAVIRUSES IN HUMAN MILK: THE PRODUCTION OF
2 N AND CHARACTERIZATION OF MOUSE MAMMARY TUMOR VIRUS
398 PARTICLES: MOUSE MAMMARY TUMOR VIRUS NUCLEOPROTEIN
277 AMMARY CARCINOMAS IN MICE./ IMMUNOLOGICAL
278 MAMMARY TUMORS AND EMBRYONIC ANTIGENS/ SEARCH FOR
200 NTIGENIC CROSS-REACTIVITY OF ONCOGENIC RNA VIRUSES:
354 PECIFICITY OF CELL-MEDIATED IMMUNITY IN MOUSE-HUMAN
200 EN MOUSE MAMMARY TUMOR VIRU/ STUDIES ON ANTIGENIC
350 HY WITH MURINE MAMMARY CARCINOMAS: LOCATION OF /
128
269 ICAL DEPRESSION BY SELECTIVE IMMUNOSUPPRESSION WITH
232 ORMAL MICE./ VIRUS-DEPENDENT
233 CHARACTERIZATION OF
261 2 HISTOCOMPATIBILITY ON GENERATION OF CELL-MEDIATED
227 ERA OF TUMOR-BEARING MICE THAT MEDIATES SPLEEN CELL
130 NODULE OUTGROWTH LINES TRANSPLANTED INTO BALB/CF.
103 NODULES IN VIRGIN AND HORMONE-STIMULATED BALB/C F.
141 BRIEF COMMUNICATION./ BIOACTIVITY OF
4 QUENCES NOT TRANSMITTED AS GERMINAL PROVIRUS IN THE
134 CARCINOGENIC EFFECTS OF ORAL DIETHYLSTILBESTROL ON
391 IVO OXIDATION OF GLUCOSE-1-14C AND GLUCOSE-6-14C IN
261 YTOTOXICITY AGAINST VIRUS-INDUCED MAMMARY TUMORS IN
309 TUMORIGENICITY AND ISOIMMUNIZING PROPERTIES OF
37 SIS IN PRENEOPLASTIC NODULE OUTGROWTH OF BALB/C AND
377 OPY (SEM) OF MAMMARY TUMOR VIRUS (MTV) BUDDING FROM
7 USE MAMMARY TUMOR VIRUSES IN MOUSE STRAINS RIII AND

CELL CULTURE FACTORS INFLUENCING IN VITRO EXPRESSION OF MOUSE MA
CELL CULTURE. / HIGH FREQU
CELL CULTURE. / HIGH FREQU
CELL CULTURES I. IMMUNOLOGIC AND STRUCTURAL STUDIES. / CHARACTE
CELL CULTURES OF MOUSE MAMMARY TUMORS. / "DOMES", PERIODICAL
CELL CULTURES TREATED WITH IODODEOXYURIDINE (MEETING ABSTRACT).
CELL CULTURES. / ENHANCED PRODUCTION OF MOUSE MAMMARY TUMOR VIRU
CELL CULTURES. II. BIOCHEMICAL AND BIOPHYSICAL STUDIES. / CHARA
CELL CULTURES: DEPENDENCE OF HORMONE-INDUCED CELLULAR ORGANIZAT
CELL CYTOXICITY TOWARD THE AUTOLOGOUS TUMOR. / ANTIBODY IN
CELL DENSITY-DEPENDENT GROWTH IN AGAR OF BONE MARROW CELLS FROM
CELL DEPLETION. / STIMULATION OF IMMUN
CELL FUSION ON PRODUCTION OF THE MOUSE MAMMARY TUMOR VIRUS: IMM
CELL LINE BY SCANNING ELECTRON MICROSCOPY. / SURFACE LOCALIZATIO
CELL LINE WITH THE MOUSE MAMMARY TUMOR VIRUS.
CELL LINE.
CELL LINE. / IMMUNOLOGIC ST
CELL LINE. / STIMULATION OF MAMM
CELL LINE; KINETICS OF MAMMARY TUMOR VIRUS (MTV) PRODUCTION (ME
CELL LINE-SPECIFIC CELL SURFACE COMPONENTS OF HYPOTETRAPLOID ASC
CELL LINE, DETROIT-6. / PR
CELL LINE, MCF-7. / REPLICATION OF O
CELL LINE, MCF-7. / HORMONAL STIMULATION OF
CELL LINE, VIRUS CHARACTERIZATION, AND QUANTITATION OF VIRUS PRO
CELL LINES AND CLONAL DERIVATIVES. / COMPARISON OF THE GROWTH PR
CELL LINES AND MASON-PFIZER VIRUS. / COMM
CELL LINES AND PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS IN A SERU
CELL LINES BY MORPHOLOGICAL, VIROLOGICAL, AND IMMUNOLOGICAL TECH
CELL LINES INFECTED WITH BITTNER VIRUS-CONTAINING INOCULA.
CELL LINES. / CULTIVATI
CELL LINES. / B-TYPE O
CELL PREPARATIONS FROM BOTH MTV-FREE AND MTV-INFECTED MICE.
CELL RECOGNITION BY MALIGNANT MAMMARY EPITHELIUM (MEETING ABSTRA
CELL SURFACE COMPONENTS OF HYPOTETRAPLOID ASCITES MAMMARY CARCIN
CELL SURFACE INCOMPLETE SACCHARIDE MOIETIES.
CELL SURFACE. / IDENTIFICATION OF THE MAMMARY TUMOR VIRUS ENVEL
CELL-MEDIATED CYTOTOXICITY AGAINST VIRUS-INDUCED MAMMARY TUMORS
CELL-MEDIATED IMMUNITY IN MOUSE-HUMAN CROSS-REACTIONS: FORMAL DI
CELLULAR IMMUNITY TO THE MAMMARY TUMOUR VIRUS IN MICE BEARING PR
CELLULAR IMMUNITY.
CELLULAR ORGANIZATION. / REPLICATION OF MAMMARY TUMOR VIRUS IN
CHAIN INITIATOR SITES FOR THE SYNTHESIS OF DIFFERENT CLASSES OF
CHEMOTHERAPEUTIC CONSEQUENCES. / MOLECULA
CHEMOTHERAPEUTIC RESULTS IN HUMAN AND MURINE SOLID CARCINOMA.
CONCANAVALIN A REACTIVITY. / MARKERS TO DISTINGUISH NORMAL AND N
CONCANAVALIN A TO THE ENVELOPE OF TWO MURINE RNA TUMOUR VIRUSES.
CONCOMITANT SPECIFIC IMMUNIZATION. / ACCELERATED DEVELOPMENT OF
CONTINUOUS HUMAN CANCER CELL LINES.
CONTINUOUS HUMAN CELL LINE, DETROIT-6.
CONTINUOUS HUMAN CELL LINES AND MASON-PFIZER VIRUS.
CONTINUOUS MOUSE MAMMARY TUMOR CELL LINES AND CLONAL DERIVATIVES
CORE. / THE STRUCTURE OF THE MOUSE MAMMARY
CORES (MEETING ABSTRACT). / FURTHER EVIDENCE F
CORES. / ISOLATIO
CORES? / INTRACYTOPLASMIC A
CROSS REACTIONS BETWEEN VIRUS PRODUCING AND NONVIRUS PRODUCING M
CROSS-REACTING ANTIGENICITY BETWEEN MAMMARY TUMOR VIRUS-INDUCED
CROSS-REACTIONS BETWEEN MOUSE MAMMARY TUMOR VIRUSES FROM DIFFERE
CROSS-REACTIONS: FORMAL DISCUSSION. / S
CROSS-REACTIVITY OF ONCOGENIC RNA VIRUSES: CROSS-REACTIONS BETWE
CROSSED REACTION OF HUMAN BREAST CANCER AND FIBROCYSTIC MASTOPAT
CYCLIC AMP REGULATION OF MAMMARY TUMOR VIRUS PRODUCTION.
CYTOSINE ARABINOSIDE. / CORRECTION OF A MURINE MAMMARY TUMOR VI
CYTOSTATIC ACTIVITY TO MAMMARY TUMOR CELLS OF LYMPHOCYTES FROM N
CYTOTOXIC EFFECTOR CELLS IN THE MOUSE MAMMARY TUMOR SYSTEM.
CYTOTOXICITY AGAINST VIRUS-INDUCED MAMMARY TUMORS IN C3H MICE.
CYTOXICITY TOWARD THE AUTOLOGOUS TUMOR. / ANTIBODY IN THE S
C3H AND (C3HF X BALB/C)F1 MICE. / APPEARANCE OF VIRUS PARTICLES
C3H AND C3HF MICE. / TUMOR-PRODUCING CAPABILITIES OF HYPERPLASTI
C3H AND RIII MAMMARY TUMOR VIRUSES IN VIRGIN FEMALE BALB/C MICE:
C3H AND RIII MOUSE STRAINS. / ISOLATION OF THE MOUSE MAMMARY TUM
C3H MALE MICE WITH AND WITHOUT THE MAMMARY TUMOR VIRUS.
C3H MICE. / EFFECT OF MAMMARY TUMOR VIRUS INFECTION ON IN V
C3H MICE. / ROLE OF H-2 HISTOCOMPATIBILITY ON GENERATION OF CELL
C3H MOUSE CELLS UNDERGOING "SPONTANEOUS" MALIGNANT CONVERSION IN
C3H MOUSE MAMMARY GLAND. / DNA POLYMERASE ACTIVITY AND DNA SYNTH
C3H MOUSE MAMMARY TUMOR CELLS IMMUNOLOGICALLY LABELED WITH TOBAC
C3H. / A BIOCHEMICAL APPROACH TO THE STUDY OF THE TRANSMISSION O

265 MIDE/WHOLE-BODY IRRADIATION/ALS/VIRUS-FREE (C57BL X
142 OR VIRUS. / RESPONSE OF
292 SMITTED BY EITHER PARENT./ STRAIN
171 REDUCED INCIDENCE OR SPONTANEOUS MAMMARY TUMORS IN
263 IRUS-CONTAINING TISSUES IN MAMMARY TUMOR VIRUS-FREE
310 WTH OF TRANSPLANTED MAMMARY GLAND TUMORS ARISING IN
103 IN VIRGIN AND HORMONE-STIMULATED BALB/C F. C3H AND
130 TGROWTH LINES TRANSPLANTED INTO BALB/CF. C3H AND (
153 MOUSE MAMMARY TUMOR VIRUS IN HYBRIDS FROM STRAINS
174 ANISM OF RESISTANCE TO MAMMARY TUMOR DEVELOPMENT IN
285 PHOSPHAMIDE/WHOLE-BODY IRRADIATION/ALS/VIRUS-FREE (
173 ICS OF RESISTANCE TO MAMMARY TUMOR VIRUS (MTV-S) IN
149 MAMMARY GLAND TUMORS IN SUBSTRAINS C57BL/M AND
149 MAMMARY GLAND TUMORS IN SUBSTRAINS
308 PREGNANCY DEPENDENCE OF MAMMARY TUMORS IN STRAIN
145 PREGNANCY DEPENDENCE OF MAMMARY TUMORS IN STRAIN
146 STUDIES ON
315 -BEARING BALB/C MICE IN THE ABSENCE OF A CO/ CELL
370 EPITHELIAL CELLS IN VITRO: COMPARISON OF SATURATION
29 US./ CHARACTERIZATION OF A TERMINAL
83 AN ONCORNAVIRUS BY THE CONTINUOUS HUMAN CELL LINE,
127 EFFECTS OF C-AMP AND
124 ING ABSTRACT). / EFFECTS OF C-AMP AND
123 EY CELLS./ EFFECT OF
126 ON: A TISSUE CULTURE SOURCE OF VIRUS./
121 VERY OF MOUSE MAMMARY TUMOR VIRU/ OPTIMIZATION OF
125 ENHANCED PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS IN
96 ND BY ELECTRON MICROSCOPY FO/ COMPARISONS BETWEEN
98 NA TUMOR VIRUSES: STUDIES BY LASER / HYDRODYNAMIC
133 REPRODUCTIVE TRACT OF FEMALE MICE CONTINUOUSLY FED
132 TERINE, VAGINAL, AND PROLACTIN RESPONSES TO DIETARY
134 TUMOR VIRUS./ CARCINOGENIC EFFECTS OF ORAL
41 ENDENT DNA POLYMERASE ACTIVITY IN FIVE RNA VIRUSES:
23
406 HIGH-MOLECULAR-WEIGHT
211 IMMUNOLOGIC STUDIES OF THE LOW MOLECULAR WEIGHT
19 C TRANSFORMATION OF FIBROBLASTS / PURIFICATION OF
390 S./ MOUSE MAMMARY TUMOR VIRUS
14 AL CELLS OF THE BALB/ LEVELS OF MMTV SEQUENCES IN
31 EFFECT OF LONG-TERM INCUBATION ON RNA DEPENDENT
37 E OUTGROWTH OF BALB/C AND C3H MOUSE MAMMARY GLAN/
41 UIREMENTS (MEETING ABSTRACT)./ RNA-DEPENDENT
38 (MEETING ABSTRACT)/ DETECTION OF RNA-INSTRUCTED
42 EVIDENCE FOR PARTICLES ENCAPSULATING RNA-INSTRUCTED
333 EETING ABSTR/ PARTICLES CONTAINING RNA-INSTRUCTED
32 ISOLATION AND CHARACTERIZATION OF RNA-DIRECTED
33 ISOLATION AND CHARACTERIZATION OF RNA-DIRECTED
332 WITH RNA OF HIGH MOLECULAR WEIGHT AND RNA-DIRECTED
35 CHARACTERIZATION AND SEPARATION OF VIRAL
36 Y GLAND OF BALB/C MICE./ RNA-DEPENDENT
331 PURIFICATION AND CHARACTERIZATION OF THE
26 VIRAL RNA-DEPENDENT
27 CATION AND PROPERTIES OF MURINE MAMMARY TUMOR VIRUS
28 Y TUMOR VIRUS./ RNASE H AND RNA-DIRECTED
30 MOUSE MAMMARY TUMOR VIRUS
34 MOUSE MAMMARY TUMOUR VIRUS RNA-DEPENDENT
40 CATION PREFERENCES FOR POLY(RC).OLIGO(DG)-DIRECTED
16)./
37 H MOUSE MAMMARY GLAN/ DNA POLYMERASE ACTIVITY AND
11 TUMOUR VIRUS SPECIFIC NUCLEOTIDE SEQUENCES IN MOUSE
405 ERIZATION OF INTRACYTOPLASMIC A PARTICLE-ASSOCIATED
18 POSSIBILITY OF A
24 RASES OF THE ONCOGENIC RNA VIRUSES./ SYNTHETIC
371 PRIMARY EPITHELIAL CELL
372 ES IN CELL CULTURES OF MOUSE MAMMARY TUMORS./ "
24 IRUSES./ SYNTHETIC DNA-RNA HYBRIDS AND RNA-RNA
404 ITH SPECIAL CONSIDERATION OF THE MECHANISM INVOL/
93 F THE OUTER DIMENSIONS OF ONCORNAVIRUSES BY SEVERAL
409 UCED LEUKEMIA IN ICRC MICE./ AN
163 OF IN VITRO CULTURED L1210 LEUKEMIA CELLS BY IMMUNE
377 ROM C3H MOUSE MAMMARY TUMOR CELLS IMMUN/ SCANNING
96 BY LASER BEAT FREQUENCY SPECTROSCOPY (LBFS) AND BY
1 IRUS./
92 USES FOLLOWING DIFFERENT METHODS OF PREPARATION FOR
98 ER BEAT FREQUENCY LIGHT-SCATTERING SPECTROSCOPY AND
118 PRODUCING MOUSE MAMMARY TUMOR CELL LINE BY SCANNING

C3H)F(1) HYBRIDS). / INFLUENCE OF IMMUNOSUPPRESSION ON THE GROWT
C3H-AVYFB FEMALE MICE TO A LOW ONCOGENIC, MILK-BORNE MAMMARY TUM
C3H-AVYFB MICE: NINETY PERCENT INCIDENCE OF MAMMARY TUMORS TRAN
C3H/HE MICE AFTER TREATMENT WITH POLYADENYLATE-POLYURIDYLATE.
C3H/2 HOSTS. / IMMUNOLOGY OF SPONTANEOUS MAMMARY CARCINOMAS IN M
C3HF MICE. / EFFECT OF EARLY THYMECTOMY ON GRO
C3HF MICE. / TUMOR-PRODUCING CAPABILITIES OF HYPERPLASTIC ALVEOL
C3HF X BALB/C)F1 MICE. / APPEARANCE OF VIRUS PARTICLES IN BALB/C
C57BL AND GR: BREEDING TEST OF BACKCROSS SEGREGANTS.
C57BL AND I STRAINS OF MICE. II. INHERENT DIFFERENCES BETWEEN
C57BL X C3H)F(1) HYBRIDS). / INFLUENCE OF IMMUNOSUPPRESSION ON T
C57BL/CRGL AND I/CRGL MICE. / THE GENET
C57BL/HE MICE.
C57BL/M AND C57BL/HE MICE.
DDD MICE.
DDD MICE.
DDD MOUSE WITH SPECIAL REFERENCE TO MAMMARY GLAND TUMORS.
DENSITY-DEPENDENT GROWTH IN AGAR OF BONE MARROW CELLS FROM TUMOR
DENSITY, MORPHOLOGY AND CONCANAVALIN A REACTIVITY. / MARKERS TO
DEOXYNUCLEOTIDYL TRANSFERASE ACTIVITY IN MOUSE MAMMARY TUMOR VIR
DETROIT-6. / PRODUCTION OF
DEXAMETHASONE ON MOUSE MAMMARY TUMOR VIRUS PRODUCING CELLS.
DEXAMETHASONE ON MOUSE MAMMARY TUMOR VIRUS PRODUCING CELLS (MEET
DEXAMETHASONE ON THE MOUSE MAMMARY TUMOR VIRUS GROWN IN CAT KIDN
DEXAMETHASONE STIMULATION OF MURINE MAMMARY TUMOR VIRUS EXPRESSI
DEXAMETHASONE-STIMULATED MM5MT/C1 CELLS FOR EXPRESSION AND RECO
DEXAMETHASONE-TREATED, 5-IODODEOXYURIDINE-STIMULATED MAMMARY TUM
DIAMETERS MEASURED BY LASER BEAT FREQUENCY SPECTROSCOPY (LBFS) A
DIAMETERS OF MURINE MAMMARY, ROUS SARCOMA, AND FELINE LEUKEMIA R
DIETHYLSTILBESTROL AND 17BETA-ESTRADIOL FOR 18 MONTHS (MEETING
DIETHYLSTILBESTROL IN THE MOUSE. (MEETING ABSTRACT). / U
DIETHYLSTILBESTROL ON C3H MALE MICE WITH AND WITHOUT THE MAMMARY
DIVALENT CATION REQUIREMENTS (MEETING ABSTRACT). / RNA-DEP
DNA AND THE RNA VIRUSES (MEETING ABSTRACT).
DNA ASSOCIATED WITH INTRACYTOPLASMIC A-PARTICLE INCLUSIONS.
DNA BINDING PROTEIN OF MURINE ONCORNAVIRUSES.
DNA COMPLEMENTARY TO NUCLEOTIDE SEQUENCES REQUIRED FOR NEOPLASTI
DNA IN INFECTED RAT CELLS: CHARACTERIZATION OF UNINTEGRATED FORM
DNA OF "VIRUS-" AND "HORMONE-INDUCED" MALIGNANT MAMMARY EPITHELI
DNA POLYMERASE (RDP) ACTIVITY IN MOUSE MAMMARY TUMOR VIRUS (MMTV
DNA POLYMERASE ACTIVITY AND DNA SYNTHESIS IN PRENEOPLASTIC NODUL
DNA POLYMERASE ACTIVITY IN FIVE RNA VIRUSES: DIVALENT CATION REQ
DNA POLYMERASE AND HIGH MOLECULAR WEIGHT RNA IN MALIGNANT TISSUE
DNA POLYMERASE AND HIGH MOLECULAR WEIGHT VIRUS-RELATED RNA IN HE
DNA POLYMERASE AND VIRUS-RELATED RNA IN HUMAN BREAST CANCERS (M
DNA POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS (MEETING ABSTRACT).
DNA POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS.
DNA POLYMERASE IN HUMAN BRAIN TUMORS (MEETING ABSTRACT). / PART
DNA POLYMERASE IN MOUSE MILK (MEETING ABSTRACT).
DNA POLYMERASE IN PRENEOPLASTIC NODULES AND TUMORS OF THE MAMMAR
DNA POLYMERASE OF HUMAN BREAST CANCER PARTICLES.
DNA POLYMERASE.
DNA POLYMERASE. / PURIFI
DNA POLYMERASE: ASSOCIATED ENZYMATIC ACTIVITIES OF MURINE MAMMAR
DNA POLYMERASE: PURIFICATION AND PROPERTIES (MEETING ABSTRACT).
DNA POLYMERASE: REQUIREMENTS AND PRODUCTS.
DNA SYNTHESIS BY RNA TUMOR VIRUSES AND HUMAN MILK PARTICULATES.
DNA SYNTHESIS BY RNA-CONTAINING TUMOR VIRUSES (MEETING ABSTRACT
DNA SYNTHESIS IN PRENEOPLASTIC NODULE OUTGROWTH OF BALB/C AND C3
DNA. / MAMMARY
DNA. / FURTHER CHARACT
DNA-CONTAINING MAMMARY TUMOUR VIRUS IN RED BLOOD CELLS OF MOUSE.
DNA-RNA HYBRIDS AND RNA-RNA DUPLEXES AS TEMPLATES FOR THE POLYME
DOME CULTURE OF MOUSE MAMMARY TUMORS.
DOMES", PERIODICALLY EXPANDING AND COLLAPSING SECRETORY STRUCTUR
DUPLEXES AS TEMPLATES FOR THE POLYMERASES OF THE ONCOGENIC RNA V
ELECTRON MICROSCOPE STUDIES OF MOUSE MAMMARY TUMOR VIRUS (MTV) W
ELECTRON MICROSCOPIC PROCEDURES. / A DETERMINATION O
ELECTRON MICROSCOPIC STUDY OF SPONTANEOUS AND EXPERIMENTALLY IND
ELECTRON MICROSCOPY (MEETING ABSTRACT). / IDENTIFICATION OF THE
ELECTRON MICROSCOPY (SEM) OF MAMMARY TUMOR VIRUS (MTV) BUDDING F
ELECTRON MICROSCOPY FOR MURINE MAMMARY TUMOR (MUMTV), ROUS SARCO
ELECTRON MICROSCOPY OF THE NUCLEIC ACID OF MOUSE MAMMARY TUMOR V
ELECTRON MICROSCOPY. / THE MORPHOLOGY OF MURINE ONCORNAVIR
ELECTRON MICROSCOPY. / HYDRODYNAMIC DIAMETERS OF MURINE MAMMARY,
ELECTRON MICROSCOPY. / SURFACE LOCALIZATION OF VIRUS PRODUCTION

97 DIFFUSION AND
161 TRACT)./ TRANSFORMATION OF X/GF MOUSE
278 WEEN MAMMARY TUMOR VIRUS-INDUCED MAMMARY TUMORS AND
384 INFECTION OF MINK
419 MAMMARY GLAND AS A MORPHOLOGICAL
420
125 E-TREATED, 5-IODODEOXYURIDINE-STIMULATED MAMMARY/
230 CTED BY DIFF/ SERUM FACTORS IN MAMMARY NEOPLASIA:
267 (MTV) INFECTION (MEETING ABSTRACT). /
210 PSEUDOTYPES OF VESICULAR STOMATITIS VIRUS WITH
53 RFACE./ IDENTIFICATION OF THE MAMMARY TUMOR VIRUS
206 BINDING OF CONCANAVALIN A TO THE
28 RNASE H AND RNA-DIRECTED DNA POLYMERASE: ASSOCIATED
452
451 ANCER. (PP. 49-59)/
272)./ EXPRESSION OF NORMAL MAMMARY
371 PRIMARY
53 VIRUS ENVELOPE GLYCOPRUTEIN (GP52) ON MOUSE MAMMARY
380 RINE MAMMARY TUMOR VIRUS INFECTION OF MOUSE MAMMARY
370 ARKERS TO DISTINGUISH NORMAL AND NEOPLASTIC MAMMARY
14 OF "VIRUS-" AND "HORMONE-INDUCED MALIGNANT MAMMARY
313 CELL RECOGNITION BY MALIGNANT MAMMARY
312 ROLACTIN LEVEL IN BALB/C MICE./ EFFECT OF
182 INHERITANCE OF SUSCEPTIBILITY TO
112 INFLUENCE OF HIGH DOSE OF
305 LINES AND TUMORS./ HORMONE DEPENDENCE AND
264 THE CARCINOGENIC POWER OF MAMMARY TUMOR VIRUS AFTER
72 ORGAN DISTRIBUTION OF
121 ION OF DEXAMETHASONE-STIMULATED MM5MT/C1 CELLS FOR
106 HIGH FREQUENCY VARIATION IN MAMMARY TUMOR VIRUS
151 HIGH FREQUENCY VARIATION IN MAMMARY TUMOR VIRUS
117 UMOR VIRUS (MEETING ABSTR/ SUPPRESSION OF C-TYPE
198 VIRUS IN TUMORS OF MAMMARY GLANDS IN MICE OF VAR/
270 MPHOID CELLS./
177 GENETIC ANALYSIS OF MAMMARY TUMOR INDUCTION AND
122 VARIATIONS IN PHENOTYPIC
60 D TISSUES./
116 CELL CULTURE FACTORS INFLUENCING IN VITRO
272 NEOPLASIA (MEETING ABSTRACT)./
76 : DETECTION BY MOLECULAR HYBRI/ THE PRESENCE AND
15 : DETECTION BY MOLECULAR HYBRI/ THE PRESENCE AND
396 / TRANSMISSION AND
273 LS OF MICE./
154 ARY TUMOR CELL CLONES WITH VARYING DEGREES OF VIRUS
111 REGULATION OF MOUSE MAMMARY TUMOR VIRUS GENE
126 METHASONE STIMULATION OF MURINE MAMMARY TUMOR VIRUS
374 F PRENEOPLASTIC MAMMARY NODULE OUTGROWTH IN MAMMARY
96 RINE MAMMARY TUMOR (MUMTV), ROUS SARCOMA (RSV), AND
98 AMIC DIAMETERS OF MURINE MAMMARY, ROUS SARCOMA, AND
96 (MUMTV), ROUS SARCOMA (RSV), AND FELINE LEUKEMIA (
350 OF / CROSSED REACTION OF HUMAN BREAST CANCER AND
393 HE LACTEOUS FACTOR FROM PS STRAIN MICE PERFORMED ON
12 CLEIC ACID OF MOUSE MAMMARY TUMOR VIRUS (MTV) USING
291 MAMMARY CARCINOGENESIS IN
91 PHOGENESIS./ APPLICATION OF
65 (GP52) O/ DETECTION OF THE MAJOR GLYCOPROTEINS OF
90 ICLES IN ADENOCARCINOMAS INDUCED BY IMPLANTATION OF
164 -INFECTED MOUSE MAMMARY TUMOUR CELLS. ABSENCE O/
397 -INFECTED MOUSE MAMMARY TUMOUR CELLS. ABSENCE O/
156 UORESCENCE STUDY (MEETING ABSTR/ EFFECTS OF CELL
50 EXTRINSIC LABELING OF MUMTV WITH A
166 ESISTANCE OF VIRUS FROM MURINE MAMMARY TUMORS AFTER
111 REGULATION OF MOUSE MAMMARY TUMOR VIRUS
180 S IN MICE. / HISTOCOMPATIBILITY
181 HISTOCOMPATIBILITY
76 THE PRESENCE AND EXPRESSION OF RNA TUMOR VIRUS
15 THE PRESENCE AND EXPRESSION OF RNA TUMOR VIRUS
177 MMARY TUMOR VIRUS ANTIGEN IN HORMONE-TREATED OVA/
442 THE
441 FOR HUMAN DISEASE./ INTERACTION BETWEEN VIRAL AND
175 E MAMMARY TUMOR VIRUS BY THE GR MOUSE STRAIN. II.
176
172 E (MEETING ABSTRACT)./
179 COMPARISON OF THREE MAMMARY TUMOR VIRUSES IN
422
445 THE MOLECULAR
173 RGL AND I/CRGL MICE./ THE
415 INTERNATIONAL CONFERENCE ON RNA VIRUSES AND HOST

ELECTROPHORESIS OF RNA TUMOR VIRUSES.
EMBRYO CELL CULTURES TREATED WITH IODODEOXYURIDINE (MEETING ABS
EMBRYONIC ANTIGENS: EFFECT OF IMMUNIZATION ON DEVELOPMENT OF SP
EMBRYONIC CELLS WITH THE MOUSE MAMMARY TUMOR VIRUS.
END POINT IN CARCINOGENESIS STUDIES.
ENDOGENOUS MAMMARY TUMOR VIRUSES IN MICE. (PP. 1045-1049)
ENHANCED PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS IN DEXAMETHASON
ENHANCEMENT AND ANTAGONISM OF SPLEEN CELL ACTIVITY IN VITRO DETE
ENHANCEMENT OF BLOCKING FACTOR PRODUCTION BY MAMMARY TUMOR VIRUS
ENVELOPE ANTIGENS PROVIDED BY MURINE MAMMARY TUMOR VIRUS.
ENVELOPE GLYCOPROTEIN (GP52) ON MOUSE MAMMARY EPITHELIAL CELL SU
ENVELOPE OF TWO MURINE RNA TUMOUR VIRUSES.
ENZYMATIC ACTIVITIES OF MURINE MAMMARY TUMOR VIRUS. /
EPIDEMIOLOGIC ASPECTS OF MAMMARY TUMOURS.
EPIDEMIOLOGY OF CANCER AND HOST SUSCEPTIBILITY FACTORS: BREAST C
EPITHELIAL CELL ANTIGENS IN MAMMARY NEOPLASIA (MEETING ABSTRACT
EPITHELIAL CELL DOME CULTURE OF MOUSE MAMMARY TUMORS.
EPITHELIAL CELL SURFACE. / IDENTIFICATION OF THE MAMMARY TUMOR
EPITHELIAL CELLS IN VITRO (MEETING ABSTRACT). / MU
EPITHELIAL CELLS IN VITRO: COMPARISON OF SATURATION DENSITY, MOR
EPITHELIAL CELLS OF THE BALB/C MOUSE (MEETING ABSTRACT). / LEVE
EPITHELIUM (MEETING ABSTRACT).
ERGOCORNINE ON TRANSPLANTED MAMMARY TUMOR GROWTH AND PITUITARY P
ERYTHROCYTE-BORN BITTNER VIRUS IN MICE.
ESTRADIOL ON THE ICRC MOUSE BEARING TRANSPLANTED MAMMARY TUMORS.
ESTRADIOL RECEPTORS IN THE D SERIES OF MAMMARY NODULE OUTGROWTH
ETHYLENE OXIDE TREATMENT: DISTRIBUTION OF VIRAL PARTICLES. / INC
EXOGENOUS MURINE MAMMARY TUMOUR VIRUS AS DETERMINED BY BIOASSAY.
EXPRESSION AND RECOVERY OF MOUSE MAMMARY TUMOR VIRUS WITH HIGH R
EXPRESSION IN CELL CULTURE.
EXPRESSION IN CELL CULTURE.
EXPRESSION IN LARGE-SCALE IN VITRO PRODUCTION OF MOUSE MAMMARY T
EXPRESSION OF INDIVIDUAL PROTEINS OF MOUSE MAMMARY GLAND CANCER
EXPRESSION OF MAMMARY TUMOR VIRUS ANTIGEN ON THE MEMBRANES OF LY
EXPRESSION OF MAMMARY TUMOR VIRUS ANTIGEN IN HORMONE-TREATED OVA
EXPRESSION OF MMTV IN MOUSE MAMMARY TUMOR-DERIVED CELL CLONES.
EXPRESSION OF MOUSE MAMMARY TUMOR VIRAL POLYPEPTIDES IN MILKS AN
EXPRESSION OF MOUSE MAMMARY TUMOR VIRUS.
EXPRESSION OF NORMAL MAMMARY EPITHELIAL CELL ANTIGENS IN MAMMARY
EXPRESSION OF RNA TUMOR VIRUS GENES IN NORMAL AND INFECTED CELLS
EXPRESSION OF RNA TUMOR VIRUS GENES IN NORMAL AND INFECTED CELLS
EXPRESSION OF THE LEUKEMIA INDUCING AGENT IN BALB/CF(RIII) MICE.
EXPRESSION OF THY 1 ANTIGEN IN NORMAL AND NEOPLASTIC MAMMARY CEL
EXPRESSION. / MURINE MAMM
EXPRESSION.
EXPRESSION: A TISSUE CULTURE SOURCE OF VIRUS. / DEXA
FAT PADS OF BALB/C MICE IN ORGAN CULTURE. / PROLIFERATION O
FELINE LEUKEMIA (FELV) VIRUSES (MEETING ABSTRACT). / COMPARISON
FELINE LEUKEMIA RNA TUMOR VIRUSES: STUDIES BY LASER BEAT FREQUEN
FELV) VIRUSES (MEETING ABSTRACT). / COMPARISONS BETWEEN DIAMETE
FIBROCYSTIC MASTOPATHY WITH MURINE MAMMARY CARCINOMAS: LOCATION
FICOLL GRADIENTS. / BIOLOGICAL ACTIVITY OF DIFFERENT ZONES OBTAI
FLUORESCENCE MICROSCOPY. / IDENTIFICATION OF THE NU
FOSTER-NURSED X/GF MICE.
FREEZE-DRYING INTACT CELLS TO STUDIES OF MURINE ONCORNAVIRUS MOR
FRIEND LEUKEMIA VIRUS (GP71) AND THE MURINE MAMMARY TUMOR VIRUS
FUKU CELLS. / ATYPICAL C PART
FUSION OF XC RAT SARCOMA CELLS INDUCED BY MURINE LEUKAEMIA VIRUS
FUSION OF XC RAT SARCOMA CELLS INDUCED BY MURINE LEUKAEMIA VIRUS
FUSION ON PRODUCTION OF THE MOUSE MAMMARY TUMOR VIRUS: IMMUNOFL
GALACTOSE OXIDASE-TRITIATED BOROHYDRIDE METHOD.
GAMMA IRRADIATION. / RADIOR
GENE EXPRESSION.
GENES (THE H-2 COMPLEX) AND SUSCEPTIBILITY TO MAMMARY TUMOR VIRU
GENES AND SUSCEPTIBILITY TO MAMMARY TUMOR VIRUS (MTV) IN MICE.
GENES IN NORMAL AND INFECTED CELLS: DETECTION BY MOLECULAR HYBR
GENES IN NORMAL AND INFECTED CELLS: DETECTION BY MOLECULAR HYBR
GENETIC ANALYSIS OF MAMMARY TUMOR INDUCTION AND EXPRESSION OF MA
GENETIC ASPECTS OF HUMAN CANCER.
GENETIC FACTORS IN MURINE MAMMARY CANCER: POSSIBLE IMPLICATIONS
GENETIC STUDIES. / TRANSMISSION OF TH
GENETIC TRANSMISSION OF MAMMARY TUMOUR VIRUS BY GR MICE.
GENETIC TRANSMISSION OF VIRUSES THAT INCITE MAMMARY TUMOR IN MIC
GENETICALLY SIMILAR SUSCEPTIBLE MICE.
GENETICS OF CANCER.
GENETICS OF HUMAN CANCER AND ITS ETIOLOGIC IMPLICATIONS.
GENETICS OF RESISTANCE TO MAMMARY TUMOR VIRUS (MTV-S) IN C57BL/C
GENOME IN ONCOGENESIS.

413 CE. / MAMMARY TUMOR VIRUS AND HOST
318 AN BREAST TUMOUR RNA AND MOUSE MAMMARY TUMOUR VIRUS
25 TES AND OTHER ONCORNAVIRU/ MASON-PFIZER VIRUS RNA
5 PARTIAL RNA SEQUENCE ANALYSI/ DIFFERENCES BETWEEN
3 VISUALIZATION OF THE
4 SE MAMMARY TUMOR VIRUS SEQUENCES NOT TRANSMITTED AS
84 SURFACE STRUCTURE OF VIRIONS BUDDING FROM L1210(V)
221 RUS (MTV)-SPECIFIC IMMUNE COMPLEX DEPOSITS IN RENAL
107 BIOCHEMICAL AND PHYSIOLOGICAL MECHANISMS IN
109 (PP. 1151-1158)/
108 AMMARY TUMOUR VIRUS PRODUCTION AFTER STIMULATION BY
110 ARY TUMOR VIRUS./
104 RUS RNA: INCREASED RATE OF SYNTHESIS OF VIRAL RN/
118 SURFACE LOCALIZATION OF VIRUS PRODUCTION ON A
391 MMARY TUMOR VIRUS INFECTION ON IN VIVO OXIDATION OF
391 INFECTION ON IN VIVO OXIDATION OF GLUCOSE-1-14C AND
54 ING ABSTRACT)./
53 IDENTIFICATION OF THE MAMMARY TUMOR VIRUS ENVELOPE
193 ECIFIC ANTIGENIC DETERMINANTS ON THE MAJOR EXTERNAL
192 ULTIPLE ANTIGENIC DETERMINANTS ON THE MAJOR SURFACE
65 MARY TUMOR VIRUS (GP52) O/ DETECTION OF THE MAJOR
59 IDENTIFICATION OF A PRECURSOR PROTEIN TO THE MAJOR
66 US, AND MASON-PFIZER MONKEY VIRUS/ SIALYLATION OF
58 AMMARY TUMOR VIRUS. II. IDENTIFICATION OF TWO MAJOR
61 OF THE MOUSE MAMMARY TUMOR VIRUS: POLYPEPTIDES AND
352 HUMAN BREAST CANCER WITH MOUSE MAMMARY TUMOR VIRUS,
352 ST CANCER WITH MOUSE MAMMARY TUMOR VIRUS, GP-52 AND
53 OF THE MAMMARY TUMOR VIRUS ENVELOPE GLYCOPROTEIN (
65 A VIRUS (GP71) AND THE MURINE MAMMARY TUMOR VIRUS (
197 APY (MEETIN/ MOUSE MAMMARY TUMOR VIRUS ANTIGEN (
65 THE MAJOR GLYCOPROTEINS OF FRIEND LEUKEMIA VIRUS (
213 OF MAMMARY TUMOR VIRUS ANTIGENS ON THE SURFACES OF
276 TUMORS, TRANSFORMED BALB/C MOUSE KIDNEY CELLS, AND
300 MAMMARY TUMOR VIRUS IN STRAIN
176 GENETIC TRANSMISSION OF MAMMARY TUMOUR VIRUS BY
177 MOR VIRUS ANTIGEN IN HORMONE-TREATED OVARIECTOMIZED
175 TRANSMISSION OF THE MAMMARY TUMOR VIRUS BY THE
143 F HYPERPLASTIC ALVEOLAR NODULES (HAN) IN THE STRAIN
99 MAMMARY-TUMOR VIRUS ACTIVITY IN BRAIN AND LIVER OF
153 MMARY TUMOR VIRUS IN HYBRIDS FROM STRAINS C57BL AND
194 SYNTHESIS OF MURINE RNA TUMOR VIRUS (ONCORNAVIRUS)
57 USE MAMMARY TUMOR VIRUS. I. CHARACTERIZATION OF TWO
312 EFFECT OF ERGOCORNINE ON TRANSPLANTED MAMMARY TUMOR
315 CE IN THE ABSENCE OF A CO/ CELL DENSITY-DEPENDENT
251 INFLUENCE OF PARABIOSIS ON TUMOUR
296 STRACT)./ INHIBITION OF
310 ./ EFFECT OF EARLY THYMECTOMY ON
285 EONATAL OR/ INFLUENCE OF IMMUNOSUPPRESSION ON THE
363 OUSE MAMMARY TUMOR CELL LINES / COMPARISON OF THE
155 S TO REPLICATE MAMMARY TUMOR VIRUS AND TO RECOGNIZE
189 N BY RADIOIMMUNOASSAY. / THE PURIFICATION OF A
180 HISTOCOMPATIBILITY GENES (THE
261 TY AGAINST VIRUS-INDUCED MAMMARY TUMORS / ROLE OF
152 RO. INCREASED MACROMOLECULAR SYNTHESES IN MOUSE AND
353 ONCORNAVIRUS-LIKE PARTICLES IN
266 WITH MAMMARY TUMOR VIRUS (MTV) INFECTION IN MICE:
70 MICE./
389 INFECTION OF CULTURED RAT
180 MAMMARY TUMOR VIRUS IN MICE. /
181 US (MTV) IN MICE./
261 GAINST VIRUS-INDUCED MAMMARY TUMORS / ROLE OF H-2
307 INFLUENCE OF MILK SOURCE ON TRANSPLANTABILITY OF
361
336 T CARCINOMA CELL LINE, MCF-7./
129 Y TUMOR VIRUS, NODULE-INDUCING VIRUS, AND PROLONGED
305 MMARY NODULE OUTGROWTH LINES AND TUMORS./
107 ICAL AND PHYSIOLOGICAL MECHANISMS IN GLUCOCORTICOID
306 GEN ON CARCINOGEN-INDUCED MAMMARY TUMO/ EFFECT OF
114 Y TUMOR VIRUS. /
101 LEVELS OF MAMMARY TUMOR VIRUS IN
274 LEVELS OF MAMMARY TUMOR VIRUS IN
369 TUMOR VIRUS IN TUMOR CELL CULTURES: DEPENDENCE OF
14 LEVELS OF MMTV SEQUENCES IN DNA OF "VIRUS-" AND "
103 TIES OF HYPERPLASTIC ALVEOLAR NODULES IN VIRGIN AND
177 ON AND EXPRESSION OF MAMMARY TUMOR VIRUS ANTIGEN IN
115 MOUSE MAMMARY TUMOR VIRUS PRODUCTION STIMULATED BY
102 AL MTV SYNTHESIS IN VITRO AND THE EFFECT OF STEROID
100 US BY CULTURED CELLS IN THE ABSENCE AND PRESENCE OF

GENOME IN THE TRANSMISSION AND CAUSATION OF MAMMARY TUMORS IN MI
GENOME. / HOMOLOGY BETWEEN HUM
GENOME: RELATIONSHIP TO THE RNA OF MORPHOLOGICALLY SIMILAR ISOLA
GENOMES OF TWO STRAINS OF MOUSE MAMMARY TUMOR VIRUS AS SHOWN BY
GENOMIC RNA FROM A B-TYPE TUMOR VIRUS (MEETING ABSTRACT).
GERMINAL PROVIRUS IN THE C3H AND RIII MOUSE STRAINS. / ISOLATION
GLN- MOUSE LEUKEMIA CELLS.
GLOMERULI OF MTV-INFECTED TUMOUR-FREE MICE. / MAMMARY TUMOUR VI
GLUCOCORTICOID HORMONE INDUCTION OF MOUSE MAMMARY TUMOR VIRUS.
GLUCOCORTICOID INDUCTION OF MURINE MAMMARY TUMOR VIRUS IN VITRO.
GLUCOCORTICOID. / RELATIONSHIP BETWEEN RECEPTOR AND M
GLUCOCORTICOID-RECEPTOR INTERACTION AND INDUCTION OF MURINE MAMM
GLUCOCORTICOID-STIMULATED ACCUMULATION OF MOUSE MAMMARY TUMOR VI
GLUCOCORTICOID-STIMULATED ONCORNAVIRUS-PRODUCING MOUSE MAMMARY T
GLUCOSE-1-14C AND GLUCOSE-6-14C IN C3H MICE. / EFFECT OF MA
GLUCOSE-6-14C IN C3H MICE. / EFFECT OF MAMMARY TUMOR VIRUS
GLYCOPEPTIDE PATTERNS OF MOUSE MAMMARY GLANDS AND TUMORS. (MEET
GLYCOPROTEIN (GP52) ON MOUSE MAMMARY EPITHELIAL CELL SURFACE.
GLYCOPROTEIN OF HIGH- AND LOW-ONCOGENIC MURINE MAMMARY TUMOR VIR
GLYCOPROTEIN OF MURINE MAMMARY TUMOR VIRUSES. / M
GLYCOPROTEINS OF FRIEND LEUKEMIA VIRUS (GP71) AND THE MURINE MAM
GLYCOPROTEINS OF MOUSE MAMMARY TUMOR VIRUS.
GLYCOPROTEINS OF MURINE MAMMARY TUMOR VIRUS, MURINE LEUKEMIA VIR
GLYCOPROTEINS WITH THE VIRAL STRUCTURE. / POLYPEPTIDES OF THE MO
GLYCOPROTEINS. / STRUCTURE
GP-52 AND GP-70. (MEETING ABSTRACT). / LEUKOCYTE MIGRATION INHI
GP-70. (MEETING ABSTRACT). / LEUKOCYTE MIGRATION INHIBITION IN
GP52) ON MOUSE MAMMARY EPITHELIAL CELL SURFACE. / IDENTIFICATION
GP52) ON THE SURFACE OF MOUSE CELLS. / DETECTION OF THE MAJOR GL
GP52): A MEANS FOR THE DETECTION OF TUMOR AND ASSESSMENT OF THER
GP71) AND THE MURINE MAMMARY TUMOR VIRUS (GP52) ON THE SURFACE O
GR ASCITES LEUKEMIA CELLS AS COMPARED WITH NORMAL ANTIGENS.
GR ASCITES LEUKEMIA CELLS. / DISTRIBUTION OF VIRUS PARTICLES AND
GR MICE IN RELATION TO AGE AND TISSUE TYPE.
GR MICE.
GR MICE. / GENETIC ANALYSIS OF MAMMARY TUMOR INDUCTION AND EXPRE
GR MOUSE STRAIN. II. GENETIC STUDIES.
GR MOUSE. / OCCURRENCE AND PRENEOPLASTIC SIGNIFICANCE O
GR STRAIN MICE.
GR: BREEDING TEST OF BACKCROSS SEGREGANTS. / MOUSE MA
GROUP-SPECIFIC ANTIGENS. / SITES OF
GROUP-SPECIFIC ANTIGENS. / POLYPEPTIDES OF THE MO
GROWTH AND PITUITARY PROLACTIN LEVEL IN BALB/C MICE. /
GROWTH IN AGAR OF BONE MARROW CELLS FROM TUMOR-BEARING BALB/C MI
GROWTH IN TUMOUR BEARING ANIMALS.
GROWTH OF MOUSE MAMMARY CARCINOMA BY STREPTOVARICIN (MEETING AB
GROWTH OF TRANSPLANTED MAMMARY GLAND TUMORS ARISING IN C3HF MICE
GROWTH OF TRANSPLANTS OF SPONTANEOUS MAMMARY TUMOURS IN MICE. (N
GROWTH PROPERTIES IN VITRO AND TRANSPLANTABILITY OF CONTINUOUS M
GROWTH-INHIBITORY CONTACT SIGNALS IN VITRO. / RELATIONSHIP BETWE
GS ANTIGEN OF THE MURINE MAMMARY TUMOR VIRUS AND ITS QUANTITATIO
H-2 COMPLEX) AND SUSCEPTIBILITY TO MAMMARY TUMOR VIRUS IN MICE.
H-2 HISTOCOMPATIBILITY ON GENERATION OF CELL-MEDIATED CYTOTOXICI
HAMSTER KIDNEY CELLS; PRODUCTION OF B- AND C-PARTICLES IN THE MO
HELA CELLS. II. IMMUNOLOGICAL CHARACTERIZATION OF THE VIRUS.
HEMAGGLUTININ RESPONSE AND ALLOGRAFT SURVIVAL. / IMMUNOLOGIC DEF
HEMIC CELL-ASSOCIATED MAMMARY TUMOR VIRUS ACTIVITY IN BALB/CF3H
HEPATOMA CELLS BY MOUSE MAMMARY TUMOR VIRUS.
HISTOCOMPATIBILITY GENES (THE H-2 COMPLEX) AND SUSCEPTIBILITY TO
HISTOCOMPATIBILITY GENES AND SUSCEPTIBILITY TO MAMMARY TUMOR VIR
HISTOCOMPATIBILITY ON GENERATION OF CELL-MEDIATED CYTOTOXICITY A
HISTOCOMPATIBLE MAMMARY TUMOURS IN MICE.
HISTOLOGICAL STUDY OF IRON DEPOSITS IN MAMMARY GLANDS OF MICE.
HORMONAL STIMULATION OF A VIRUS-RELATED ANTIGEN IN A HUMAN BREAS
HORMONAL STIMULATION ON THE TUMOR-PRODUCING CAPABILITIES OF THE
HORMONE DEPENDENCE AND ESTRADIOL RECEPTORS IN THE D SERIES OF MA
HORMONE INDUCTION OF MOUSE MAMMARY TUMOR VIRUS. / BIOCHEM
HORMONE STIMULATION, DOSE, AND TIME OF ADMINISTRATION OF CARCINO
HORMONE SYNERGISM IN THE IN VITRO PRODUCTION OF THE MOUSE MAMMAR
HORMONE-DEPENDENT AND -INDEPENDENT MOUSE MAMMARY TUMOR CELLS.
HORMONE-DEPENDENT AND -INDEPENDENT MOUSE MAMMARY TUMOR CELLS.
HORMONE-INDUCED CELLULAR ORGANIZATION. / REPLICATION OF MAMMARY
HORMONE-INDUCED MALIGNANT MAMMARY EPITHELIAL CELLS OF THE BALB/
HORMONE-STIMULATED BALB/C F. C3H AND C3HF MICE. / TUMOR-PRODUCIN
HORMONE-TREATED OVARIECTOMIZED GR MICE. / GENETIC ANALYSIS OF MA
HORMONES AND POLYAMINES IN CELLS GROWN IN SEMI-SYNTHETIC IN VITR
HORMONES ON VIRUS PRODUCTION. / CONDITIONS FOR OPTIM
HORMONES: ASSAY BY MOLECULAR HYBRIDIZATION. / PRODUCTION OF MOUS

322 ON OF RNA TUMOR VIRUSES AND VIRUS-LIKE PARTICLES IN
64 EFFECT OF
40 DG)-DIRECTED DNA SYNTHESIS BY RNA TUMOR VIRUSES AND
325 TION OF HIGH-MOLECULAR-WEIGHT RNA IN PARTICLES FROM
342 MUMTV, 734B AND A VIRUS-LIKE PARTICLE ISOLATED FROM
439 OUSE MAMMARY TUMOUR VIRUS AND OF PARTICLES FOUND IN
323 FURTHER EVIDENCE FOR ONCORNAVIRUSES IN
255 INCOMPLETE SACCHARIDE MOIETIES. /
254 TETRAPLOID ASCITES MAMMARY CARCINOMA CELLS INDUCING
438 COMMENTS ON THE USE OF ANIMAL MODELS AND MOLECULAR
322 R VIRUSES AND VIRUS-LIKE PARTICLES IN HUMAN MILK BY
21 MAEDI AND RNA TUMOR VIRUSES AS STUDIED BY MOLECULAR
100 BSENCE AND PRESENCE OF HORMONES: ASSAY BY MOLECULAR
15 NORMAL AND INFECTED CELLS: DETECTION BY MOLECULAR
76 NORMAL AND INFECTED CELLS: DETECTION BY MOLECULAR
24 THE ONCOGENIC RNA VIRUSES./ SYNTHETIC DNA-RNA
153 GREGANTS./ MOUSE MAMMARY TUMOR VIRUS IN
285 E-BODY IRRADIATION/ALS/VIRUS-FREE (C57BL X C3H)F(1)
143 OCCURRENCE AND PRENEOPLASTIC SIGNIFICANCE OF
103 ALB/C F. C3H AND/ TUMOR-PRODUCING CAPABILITIES OF
169 NBRED STRAINS AND T/ MAMMARY TUMORS, PLAQUES, AND
375 NG ABSTRACT). / CHEMICAL CARCINOGEN-INDUCED
254 CELL LINE-SPECIFIC CELL SURFACE COMPONENTS OF
409 SPONTANEOUS AND EXPERIMENTALLY INDUCED LEUKEMIA IN
112 INFLUENCE OF HIGH DOSE OF ESTRADIOL ON THE
221 R-FREE MICE./ MAMMARY TUMOUR VIRUS (MTV)-SPECIFIC
163 IRIONS OF IN VITRO CULTURED L1210 LEUKEMIA CELLS BY
250 Y TUMOR ANTIGENS./ EFFECT OF
257 PLETION. / STIMULATION OF
258 EFFECT OF SPECIFIC SOLUBLE TUMOR ANTIGENS ON
231 EN CELL PREPARATIONS FROM / IN VITRO DETECTION OF
250 EFFECT OF IMMUNE MANIPULATION ON NATURAL
191 NCER./ IN VITRO
354 SPECIFICITY OF CELL-MEDIATED
226 NATURAL
450 IS THERE EVIDENCE THAT
212 ND LOW MAMMARY TUMOR INCIDENCE./ AUTOGENOUS
214 MARY TUMOURS./ CELLULAR
237 OF T AND SUPPRESSOR CELLS IN MTV-DIRECTED CELLULAR
278 D MAMMARY TUMORS AND EMBRYONIC ANTIGENS: EFFECT OF
248 FURTHER
239 EJECTION OF SYNGENEIC MAMMARY TUMOR CELLS FOLLOWING
242 PREVENTION OF ACCELERATION BY CONCOMITANT SPECIFIC
265 ALTERATION OF
280 SE LINE CBA/BLN./ IMMUNOFLUORESCENCE AND
79 UMOR VIRUS (MTV) AND MOUSE LEUKEMIA VIRUS (MULV) BY
280 D MAMMARY TUMORS IN MOUSE LINE CBA/BLN./
156 ON ON PRODUCTION OF THE MOUSE MAMMARY TUMOR VIRUS:
394 C-TYPE ONCORNAVIRUSES AS DETERMINED BY DOUBLE STAIN
219 S IN MICE TO INTRACYTOPLASMIC A PARTICLES (IAP) /
446 R TISSUES./
220 VIRUS ONCOGENESIS AND TUMOR
263 UNOLOGY OF SPONTANEOUS MAMMARY CARCINOMAS IN MICE:
281 F BALB/C MICE FREE OF THE MAMMARY/ STUDIES ON THE
253 RY C/ DIFFERENTIAL EFFECT OF NEURAMINIDASE ON THE
245 UNOTHERAPY: MODIFICATION OF TUMOR CELLS TO INCREASE
335 U MURINE MAMMARY TUMOR / PROGNOSTICALLY FAVORABLE
334 UMTV-LIKE CHARACTERISTICS OF HUMAN BREAST CARCINOMA
365 Y TUMOR VIRUSES FROM PRIMARY TUMOR CELL CULTURES I:
266 INFECTION IN MICE: HEMAGGLUTININ RESPONSE AND /
357 CANCER (POUSSE EVOLUTIVE) IN TUNISIA: CLINICAL AND
211 EIN OF MURINE ONCORNAVIRUSES./
346 R CELL LINE./
224 ENIC VIRUS IN THE MOUSE MAMMARY TUMOR SYSTEM./
353 ONCORNAVIRUS-LIKE PARTICLES IN HELA CELLS. II.
454
277 US PRODUCING MAMMARY CARCINOMAS IN MICE./
269 RRECTION OF A MURINE MAMMARY TUMOR VIRUS-ASSOCIATED
342 PARTICLE ISOLATED FROM HUMAN MILK./
44 REVERSE TRANSCRIPTASE OF RNA TUMOR VIRUSES:
209
68 KEMIA CELL LINES BY MORPHOLOGICAL, VIROLOGICAL, AND
414 CANCER IN THE MOUSE./ REGULATION OF
377 US (MTV) BUDDING FROM C3H MOUSE MAMMARY TUMOR CELLS
424
263 ICITY OF MAMMARY TUMOR VIRUS-CONTAINING TISSUES /
201 ANTIGENICITY OF MAMMARY TUMOR VIRUS OBTAINED FRO/
447

HUMAN MILK BY HYBRIDIZATION TO POLYADENYLIC ACID SEQUENCES.
HUMAN MILK ON THE MOUSE MAMMARY TUMOR VIRUS.
HUMAN MILK PARTICULATES. / CATION PREFERENCES FOR POLY(RC).OLIGO
HUMAN MILK. / DETEC
HUMAN MILK. / IMMUNOLOGICAL RELATIONSHIPS BETWEEN
HUMAN MILK. (PP. 377-388) / PROPERTIES OF THE M
HUMAN MILK: THE PRODUCTION OF CORES (MEETING ABSTRACT).
HUMORAL REACTIONS IN SYNGENEIC HOSTS AGAINST TUMOR CELL SURFACE
HUMORAL REACTIONS IN THE SYNGENEIC HOST. / CELL LINE-SPECIFIC CE
HYBRIDIZATION IN THE SEARCH FOR HUMAN TUMOR VIRUSES. / OF BIRDS
HYBRIDIZATION TO POLYADENYLIC ACID SEQUENCES. / QUANTITATION OF
HYBRIDIZATION. / THE RELATIONSHIP OF VISNA,
HYBRIDIZATION. / PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS BY CULT
HYBRIDIZATION. / THE PRESENCE AND EXPRESSION OF RNA TUMOR VIRUS
HYBRIDIZATION. / THE PRESENCE AND EXPRESSION OF RNA TUMOR VIRUS
HYBRIDS AND RNA-RNA DUPLEXES AS TEMPLATES FOR THE POLYMERASES OF
HYBRIDS FROM STRAINS C57BL AND GR: BREEDING TEST OF BACKCROSS SE
HYBRIDS). / INFLUENCE OF IMMUNOSUPPRESSION ON THE GROWTH OF TRAN
HYPERPLASTIC ALVEOLAR NODULES (HAN) IN THE STRAIN GR MOUSE.
HYPERPLASTIC ALVEOLAR NODULES IN VIRGIN AND HORMONE-STIMULATED B
HYPERPLASTIC ALVEOLAR NODULES IN VARIOUS COMBINATIONS OF MOUSE I
HYPERPLASTIC NODULES IN WHOLE MAMMARY GLAND ORGAN CULTURE (MEETI
HYPOTETRAPLOID ASCITES MAMMARY CARCINOMA CELLS INDUCING HUMORAL
ICRC MICE. / AN ELECTRON MICROSCOPIC STUDY OF
ICRC MOUSE BEARING TRANSPLANTED MAMMARY TUMORS.
IMMUNE COMPLEX DEPOSITS IN RENAL GLOMERULI OF MTV-INFECTED TUMOU
IMMUNE ELECTRON MICROSCOPY (MEETING ABSTRACT). / IDENTIFICATION
IMMUNE MANIPULATION ON NATURAL IMMUNE RESPONSES TO MURINE MAMMAR
IMMUNE MECHANISMS AGAINST MAMMARY TUMORS BY INCOMPLETE T CELL DE
IMMUNE RESPONSES TO MAMMARY TUMORS IN MICE (MEETING ABSTRACT).
IMMUNE RESPONSES TO MTV-INDUCED MAMMARY TUMORS: ACTIVITY OF SPLE
IMMUNE RESPONSES TO MURINE MAMMARY TUMOR ANTIGENS.
IMMUNE RESPONSES TO VIRAL AND TUMOR ANTIGENS IN MURINE BREAST CA
IMMUNITY IN MOUSE-HUMAN CROSS-REACTIONS: FORMAL DISCUSSION.
IMMUNITY IN THE ONCORNAVIRUS-INFECTED MOUSE.
IMMUNITY INFLUENCES TUMOR-HOST BALANCE IN BREAST CANCER?
IMMUNITY TO MOUSE MAMMARY TUMOR VIRUS IN MOUSE STRAINS OF HIGH A
IMMUNITY TO THE MAMMARY TUMOUR VIRUS IN MICE BEARING PRIMARY MAM
IMMUNITY. / THE ROLE
IMMUNIZATION ON DEVELOPMENT OF SPONTANEOUS MAMMARY TUMORS. / SEA
IMMUNIZATION STUDIES WITH MAMMARY TUMOR VIRUS.
IMMUNIZATION WITH KILLED MOUSE MAMMARY TUMOR VIRUS (MUMTV).
IMMUNIZATION. / ACCELERATED DEVELOPMENT OF TRANSPLANTED MAMMARY
IMMUNOCOMPETENCE BY MAMMARY TUMOR VIRUS.
IMMUNOELECTRON MICROSCOPY OF VIRUS-INDUCED MAMMARY TUMORS IN MOU
IMMUNOELECTRON MICROSCOPY. / STUDIES ON MOUSE MAMMARY T
IMMUNOFLUORESCENCE AND IMMUNOELECTRON MICROSCOPY OF VIRUS-INDUCE
IMMUNOFLUORESCENCE STUDY (MEETING ABSTRACT). / EFFECTS OF CELL
IMMUNOFLUORESCENCE. / LACK OF INTERFERENCE IN ANTIGEN PRODUCTIO
IMMUNOFLUORESCENT DETECTION OF SPONTANEOUSLY OCCURRING ANTIBODIE
IMMUNOGENICITY AND MUMTV-LIKE ANTIGENICITY OF HUMAN BREAST CANCE
IMMUNOGENICITY IN THE MOUSE MAMMARY TUMOR SYSTEM.
IMMUNOGENICITY OF MAMMARY TUMOR VIRUS-CONTAINING TISSUES IN MAMM
IMMUNOGENICITY OF PRENEOPLASTIC AND NEOPLASTIC MAMMARY TISSUES O
IMMUNOGENICITY OF VIRAL ASSOCIATED AND PRIVATE ANTIGENS OF MAMMA
IMMUNOGENICITY. / EXPERIMENTAL CANCER IMM
IMMUNOGENS OF HUMAN BREAST CANCER TISSUE: ANTIGENIC SIMILARITY T
IMMUNOGENS. / M
IMMUNOLOGIC AND STRUCTURAL STUDIES. / CHARACTERIZATION OF MOUSE
IMMUNOLOGIC DEFICIENCY ASSOCIATED WITH MAMMARY TUMOR VIRUS (MTV)
IMMUNOLOGIC FEATURES (MEETING ABSTRACT). / FULMINATING BREAST
IMMUNOLOGIC STUDIES OF THE LOW MOLECULAR WEIGHT DNA BINDING PROT
IMMUNOLOGIC STUDY OF AN ONCORNAVIRUS ISOLATED FROM A HUMAN CANCE
IMMUNOLOGICAL ASPECTS OF THE RELATIONSHIP BETWEEN HOST AND ONCOG
IMMUNOLOGICAL CHARACTERIZATION OF THE VIRUS.
IMMUNOLOGICAL CONTROL OF BREAST CANCER: DISCUSSION.
IMMUNOLOGICAL CROSS REACTIONS BETWEEN VIRUS PRODUCING AND NONVIR
IMMUNOLOGICAL DEPRESSION BY SELECTIVE IMMUNOSUPPRESSION WITH CYT
IMMUNOLOGICAL RELATIONSHIPS BETWEEN MUMTV, 734B AND A VIRUS-LIKE
IMMUNOLOGICAL RELATIONSHIPS.
IMMUNOLOGICAL STUDIES ON MOUSE MAMMARY TUMORS AND LEUKEMIA.
IMMUNOLOGICAL TECHNIQUES. / IDENTIFICATION OF THE VIRIONS IN THE
IMMUNOLOGICAL TUMOR-HOST RELATIONSHIPS IN VIRUS-INDUCED MAMMARY
IMMUNOLOGICALLY LABELED WITH TOBACCO MOSAIC VIRUS (TMV) (MEETING
IMMUNOLOGY OF MAMMARY GLAND CANCER OF THE MOUSE.
IMMUNOLOGY OF SPONTANEOUS MAMMARY CARCINOMAS IN MICE: IMMUNOGEN
IMMUNOLOGY OF THE MOUSE MAMMARY TUMOR VIRUS: COMPARISON OF THE
IMMUNOLOGY: BREAST CANCER.

408 MOUSE MAMMARY TUMOR TISSUE CULTURE CELLS (MEETI/
204 LOCALIZATION OF VIRAL ANTIGENS, DETERMINED BY
249 GENIC VIRUS./ EFFECT OF TRANSIENT
285 MMARY TUMOURS IN MICE. (NEONATAL OR/ INFLUENCE OF
269 US-ASSOCIATED IMMUNOLOGICAL DEPRESSION BY SELECTIVE
240 ESIDUE (MER) FRACTION OF BCG: SOLID TUMORS./
243 ACTIVE SPECIFIC
238
246 MODIFIED TUMOR CELLS IN THE
244 ACTIVE SPECIFIC
245 ICITY. / EXPERIMENTAL CANCER
379 TISSUE CULTURE./
289 OTAL LAPSED TIME./ MOUSE MAMMARY TUMOR VIRUS
386 (MEETING ABSTRACT). / OBSERVATIONS ON THE
17 VIRUS PRODUCTION AND THE EFFECT OF RNA AND PROTEIN
162 NS FOR AN RNA TUMO/ INDEPENDENT POLYPEPTIDE CHAIN
397 US-INFECTED MOUSE MAMMARY TUMOUR CELLS. ABSENCE OF
164 US-INFECTED MOUSE MAMMARY TUMOUR CELLS. ABSENCE OF
394 -TYPE ONCORNAVIRUSES AS DETERMINED BY DO/ LACK OF
170 TANEOUS MAMMARY CARCINOMA OF MICE BY TREATMENT WITH
268 ABSTRACT)./ STUDIES ON
183 A LOCUS AFFECTING CIRCULATING
402 LES PRODUCED IN MURINE MOP/ RELATIONSHIPS BETWEEN
399 OCALIZATION OF MOUSE MAMMARY TUMOR VIRUS ANTIGEN ON
405 FURTHER CHARACTERIZATION OF
219 ON OF SPONTANEOUSLY OCCURRING ANTIBODIES IN MICE TO
401 AMMARY TUMOR VIRUS (MMTV) POLYPEPTIDE PRECURSORS IN
407 MAMMARY TUMOR VIRUS-INFECTED MICE THAT REACTS WITH
400 MOUSE MAMMARY TUMOR VIRUS POLYPEPTIDE PRECURSORS IN
398 ROTEIN CORES?/
406 HIGH-MOLECULAR-WEIGHT DNA ASSOCIATED WITH
403 CTED CHIMPANZEE LUNG CELLS (SFRE:/ OBSERVATION OF
408 CULTURE CELLS (MEETI/ IMMUNOPEROXIDASE STUDIES OF
349 RUS. / SPECIFICITY OF HUMAN ANTIBODIES TO
87 THE EVOLUTION OF MAMMARY TUMOR VIRUS IN THE MOUSE:
303 MOUSE MAMMARY TISS/ NEOVASCULARIZATION INDUCED BY
161 ION OF X/GF MOUSE EMBRYO CELL CULTURES TREATED WITH
168 TH BLOOD CELLS AND MAMMAR/ DIFFERENTIAL EFFECT OF
361 HISTOLOGICAL STUDY OF
241 ION ON THE SURVIVAL OF MICE CARRYING MAMMARY TUMOUR
309 OUS" MALIGNANT CONVERSION IN / TUMORIGENICITY AND
74 MAMMARY TUMOR VIRUS (MTV) IN DIFFERENT GRADIENT/
387 EXPERIMENTAL INFECTION OF A CAT
388 DETECTION OF MOUSE MAMMARY TUMOR VIRUS IN CAT
123 ASONE ON THE MOUSE MAMMARY TUMOR VIRUS GROWN IN CAT
152 EASED MACROMOLECULAR SYNTHESES IN MOUSE AND HAMSTER
276 S IN MOUSE MAMMARY TUMORS, TRANSFORMED BALB/C MOUSE
301 SPONTANEOUS
279 MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGENICITY OF
377 FROM C3H MOUSE MAMMARY TUMOR CELLS IMMUNOLOGICALLY
50 METHOD. / EXTRINSIC
393 FERENT ZONES OBTAINED BY ULTRACENTRIFUGATION OF THE
67 RISTICS OF SOME MURINE RNA TUMOR VIRUSES STUDIED BY
98 , AND FELINE LEUKEMIA RNA TUMOR VIRUSES: STUDIES BY
96 OPY FO/ COMPARISONS BETWEEN DIAMETERS MEASURED BY
13 POPULATION OF MOUSE MAMMARY GLANDS INFECTED WITH A
164 FUSION OF XC RAT SARCOMA CELLS INDUCED BY MURINE
397 FUSION OF XC RAT SARCOMA CELLS INDUCED BY MURINE
321 ECULAR WEIGHT VIRUS-RELATED RNA./ HUMAN
96 MMARY TUMOR (MUMTV), ROUS SARCOMA (RSV), AND FELINE
378 R VIRUS-CONTAINING INOCULA./ RELEASE OF
68 NTIFICATION OF THE VIRIONS IN THE IN VITRO L1210(V)
213 TUMOR VIRUS ANTIGENS ON THE SURFACES OF GR ASCITES
163 N OF THE BUDDING VIRIONS OF IN VITRO CULTURED L1210
279 UMOR VIRUS-ASSOCIATED ANTIGENICITY OF L-1210 MURINE
84 RUCTURE OF VIRIONS BUDDING FROM L1210(V) GLN- MOUSE
276 ANSFORMED BALB/C MOUSE KIDNEY CELLS, AND GR ASCITES
275 NDUCED AND A NORMAL ANTIGEN ON THE SURFACE OF MOUSE
409 PIC STUDY OF SPONTANEOUS AND EXPERIMENTALLY INDUCED
396 TRANSMISSION AND EXPRESSION OF THE
178 BALB/CFRIII: A NEW HIGH MAMMARY-TUMOR AND HIGH
98 AMETERS OF MURINE MAMMARY, ROUS SARCOMA, AND FELINE
65 DETECTION OF THE MAJOR GLYCOPROTEINS OF FRIEND
79 TUDIES ON MOUSE MAMMARY TUMOR VIRUS (MTV) AND MOUSE
202 NTIGENS OF THE MOUSE MAMMARY TUMOR (MTV) AND MURINE
395 RESENCE AND TRANSMISSION OF MAMMARY TUMOR VIRUS AND
66 GLYCOPROTEINS OF MURINE MAMMARY TUMOR VIRUS, MURINE
209 IMMUNOLOGICAL STUDIES ON MOUSE MAMMARY TUMORS AND

IMMUNOPEROXIDASE STUDIES OF INTRACYTOPLASMIC TYPE A PARTICLES IN
IMMUNOPEROXIDASE, IN MAMMARY ADENOCARCINOMA IN MICE.
IMMUNOSUPPRESSION ON HOST RESPONSE TO NEONATALLY INTRODUCED ONCO
IMMUNOSUPPRESSION ON THE GROWTH OF TRANSPLANTS OF SPONTANEOUS MA
IMMUNOSUPPRESSION WITH CYTOSINE ARABINOSIDE. / CORRECTION OF A
IMMUNOTHERAPEUTIC STUDIES IN MICE WITH THE METHANOL-EXTRACTION R
IMMUNOTHERAPY OF CANCER IN EXPERIMENTAL ANIMALS. (PP. 227-244)
IMMUNOTHERAPY OF CANCER WITH ANTIBODY.
IMMUNOTHERAPY OF SOLID MAMMARY TUMORS.
IMMUNOTHERAPY WITH MODIFIED TUMOR CELLS.
IMMUNOTHERAPY: MODIFICATION OF TUMOR CELLS TO INCREASE IMMUNOGEN
INFECTIVITY AND ONCOGENICITY OF THE MOUSE MAMMARY TUMOR VIRUS IN
INFECTIVITY AS A FUNCTION OF AGE AT INOCULATION, BREEDING, AND T
INFECTIVITY OF THE MOUSE MAMMARY TUMOR VIRUS IN MINK LUNG CELLS
INHIBITORS ON VIRAL SYNTHESIS. / REPLICATION OF MOUSE MAMMARY TU
INITIATOR SITES FOR THE SYNTHESIS OF DIFFERENT CLASSES OF PROTEI
INTERFERENCE BY SIMULTANEOUSLY SYNTHESIZED MAMMARY TUMOR VIRUS.
INTERFERENCE BY SIMULTANEOUSLY SYNTHESIZED MAMMARY TUMOR VIRUS.
INTERFERENCE IN ANTIGEN PRODUCTION IN VITRO BETWEEN B-TYPE AND C
INTERFERON AND POLY I:C (MEETING ABSTRACT). / INHIBITION OF SPO
INTERFERON INDUCTION BY THE MOUSE MAMMARY TUMOR VIRUS (MEETING
INTERFERON LEVELS INDUCED BY MOUSE MAMMARY TUMOR VIRUS.
INTRACISTERNAL TYPE A AND EXTRACELLULAR ONCORNAVIRUS-LIKE PARTIC
INTRACYTOPLASMIC A PARTICLE STRUCTURAL POLYPEPTIDES. (MEETING A
INTRACYTOPLASMIC A PARTICLE-ASSOCIATED DNA.
INTRACYTOPLASMIC A PARTICLES (IAP) OF MOUSE MAMMARY TUMOURS.
INTRACYTOPLASMIC A PARTICLES (MEETING ABSTRACT). / IDENTIFICATI
INTRACYTOPLASMIC A PARTICLES OF MOUSE MAMMARY TUMORS. / NATURAL
INTRACYTOPLASMIC A PARTICLES. /
INTRACYTOPLASMIC A PARTICLES: MOUSE MAMMARY TUMOR VIRUS NUCLEOP
INTRACYTOPLASMIC A-PARTICLE INCLUSIONS.
INTRACYTOPLASMIC A-TYPE PARTICLES IN BABOON C-TYPE PARTICLE INFE
INTRACYTOPLASMIC TYPE A PARTICLES IN MOUSE MAMMARY TUMOR TISSUE
INTRACYTOPLASMIC TYPE-A PARTICLES OF THE MURINE MAMMARY TUMOR VI
INTRACYTOPLASMIC VIRAL INFRAPARTICLES AND THE FORMATION OF PARTI
INTRAOCULAR XENOGRAFTS OF NORMAL, PRENEOPLASTIC, AND NEOPLASTIC
IODODEOXYURIDINE (MEETING ABSTRACT). / TRANSFORMAT
IONIZING RADIATION ON MAMMARY TUMOR VIRUS ACTIVITY ASSOCIATED WI
IRON DEPOSITS IN MAMMARY GLANDS OF MICE.
ISOGRAFTS: INJECTION OF MER AT THE TUMOUR SITE OR AT A DISTAL LO
ISOIMMUNIZING PROPERTIES OF C3H MOUSE CELLS UNDERGOING "SPONTANE
ISOPYCNIC ZONAL CENTRIFUGATION AND CHARACTERIZATION OF THE MOUSE
KIDNEY CELL LINE WITH THE MOUSE MAMMARY TUMOR VIRUS.
KIDNEY CELLS INFECTED WITH PURIFIED B PARTICLES FROM RIII MILK.
KIDNEY CELLS. / EFFECT OF DEXAMETH
KIDNEY CELLS; PRODUCTION OF B- AND C-PARTICLES IN THE MOUSE CELL
KIDNEY CELLS, AND GR ASCITES LEUKEMIA CELLS. / DISTRIBUTION OF V
KIDNEY TUMORS IN A SUBSTRAIN OF RIII/DM/SE MICE.
L-1210 MURINE LEUKEMIA CELLS.
LABELED WITH TOBACCO MOSAIC VIRUS (TMV) (MEETING ABSTRACT).
LABELING OF MUMTV WITH A GALACTOSE OXIDASE-TRITIATED BOROHYDRIDE
LACTEOUS FACTOR FROM PS STRAIN MICE PERFORMED ON FICOLL GRADIENT
LACTOPEROXIDASE IODINATION (MEETING ABSTRACT). / STRUCTURAL CHA
LASER BEAT FREQUENCY LIGHT-SCATTERING SPECTROSCOPY AND ELECTRON
LASER BEAT FREQUENCY SPECTROSCOPY (LBFS) AND BY ELECTRON MICROSC
LATENT MAMMARY TUMOR VIRUS. / ANALYSIS OF THE TRANSFER RNA
LEUKAEMIA VIRUS-INFECTED MOUSE MAMMARY TUMOUR CELLS. ABSENCE OF
LEUKAEMIA VIRUS-INFECTED MOUSE MAMMARY TUMOUR CELLS. ABSENCE OF
LEUKAEMIC CELLS CONTAIN TRANSCRIPTASE ASSOCIATED WITH A HIGH MOL
LEUKEMIA (FELV) VIRUSES (MEETING ABSTRACT). / COMPARISONS BETWE
LEUKEMIA C PARTICLES FROM MURINE CELL LINES INFECTED WITH BITTNE
LEUKEMIA CELL LINES BY MORPHOLOGICAL, VIROLOGICAL, AND IMMUNOLOG
LEUKEMIA CELLS AS COMPARED WITH NORMAL ANTIGENS. / ANTIBODY-IND
LEUKEMIA CELLS BY IMMUNE ELECTRON MICROSCOPY (MEETING ABSTRACT).
LEUKEMIA CELLS. / MAMMARY T
LEUKEMIA CELLS. / SURFACE ST
LEUKEMIA CELLS. / DISTRIBUTION OF VIRUS PARTICLES AND MAMMARY TU
LEUKEMIA CELLS. / DISTRIBUTION AND ANTIBODY-INDUCED REDISTRIBUTI
LEUKEMIA IN ICRC MICE. / AN ELECTRON MICROSCO
LEUKEMIA INDUCING AGENT IN BALB/CF(RIII) MICE.
LEUKEMIA MOUSE STRAIN.
LEUKEMIA RNA TUMOR VIRUSES: STUDIES BY LASER BEAT FREQUENCY LIGH
LEUKEMIA VIRUS (GP71) AND THE MURINE MAMMARY TUMOR VIRUS (GP52)
LEUKEMIA VIRUS (MULV) BY IMMUNOELECTRON MICROSCOPY. / S
LEUKEMIA VIRUS (MULV) IN CELLS OF CULTURES DERIVED FROM MAMMARY
LEUKEMIA VIRUS IN THE BALB/CFRIII MOUSE. / P
LEUKEMIA VIRUS, AND MASON-PFIZER MONKEY VIRUS. / SIALYLATION OF
LEUKEMIA.

449 ANTIGENS OF VIRUS-INDUCED MURINE
190 HE ROLE OF LEUKOCYTE SUBPOPULATIONS IN THE INDIRECT
343 URINE MILK SAMPLES AND HUMAN BREAST TISSUE ON HUMAN
352 MAMMARY TUMOR VIRUS, GP-52 AND GP-70. (MEETING/
190 IBITION ASSAY IN THE MAMMARY TUMOR V/ THE ROLE OF
418 ULAR BIOLOGY OF RNA TUMOR VIRUSES, ESPECIALLY AVIAN
62 INFECTED MICE: MAMMA/ STUDY OF THE COMPOSITION OF
99 MAMMARY-TUMOR VIRUS ACTIVITY IN BRAIN AND
386 NFECTIVITY OF THE MOUSE MAMMARY TUMOR VIRUS IN MINK
403 ICLES IN BABOON C-TYPE PARTICLE INFECTED CHIMPANZEE
385 RIEF COMMUNICATION: IN VITRO SUSCEPTIBILITY OF MINK
345 EAST CANCER./
218 NATURALLY OCCURRING
259 F MICE BEARING MTV INDUCED MAMMARY TUMORS AND THEIR
260 IRUS IN RELATION TO CLINICAL STATUS./
208 IN VITRO
215 ENS IN BALB// MACROPHAGE MIGRATION INHIBITION AND
341 ONG WOMEN WITH BREAST DISEASE./
232 NDENT CYTOSTATIC ACTIVITY TO MAMMARY TUMOR CELLS OF
351 ONCORNAVIRUS MARKERS ON PERIPHERAL
270 OF MAMMARY TUMOR VIRUS ANTIGEN ON THE MEMBRANES OF
163 ICATION OF THE BUDDING VIRIONS OF IN VITRO CULTURED
84 SURFACE STRUCTURE OF VIRIONS BUDDING FROM
68 IDENTIFICATION OF THE VIRIONS IN THE IN VITRO
215 MAMMARY TUMOR VIRUS ASSOCIATED ANTIGENS IN BALB//
95 RELATIONSHIP BETWEEN HYDRATION AND PROTON NUCLEAR
350 SED REACTION OF HUMAN BREAST CANCER AND FIBROCYSTIC
356 NIC, AND BIOLOGICAL CHARACTERISTICS OF PRECANCEROUS
319 -LIKE PARTICLE IN HUMAN BREAST CARCINOMA CELL LINE,
336 ATED ANTIGEN IN A HUMAN BREAST CARCINOMA CELL LINE,
271 MAMMARY TUMOR VIRUS ASSOCIATED ANTIGENS ON THE
62 MILK OF INFECTED MICE: MAMMARY TUMOR VIRUS AND THE
270 EXPRESSION OF MAMMARY TUMOR VIRUS ANTIGEN ON THE
242 SPLANTED MAMMARY TUMORS IN MICE PRETREATED WITH THE
240 IMMUNOTHERAPEUTIC STUDIES IN MICE WITH THE
51 ACT). /
35 ION AND SEPARATION OF VIRAL DNA POLYMERASE IN MOUSE
341 LYMPHOCYTE TRANSFORMATION IN VITRO TO RIII MOUSE
322 RNA TUMOR VIRUSES AND VIRUS-LIKE PARTICLES IN HUMAN
62 ECTED MICE: MAMMARY TUMOR VIRUS AND THE MEMBRANE OF
62 DS AND PROTEINS IN TWO STRUCTURES ISOLATED FROM THE
64 EFFECT OF HUMAN
40 RECTED DNA SYNTHESIS BY RNA TUMOR VIRUSES AND HUMAN
343 N INDICES./ EFFECT OF MURINE
307 URS IN MICE./ INFLUENCE OF
325 F HIGH-MOLECULAR-WEIGHT RNA IN PARTICLES FROM HUMAN
342 734B AND A VIRUS-LIKE PARTICLE ISOLATED FROM HUMAN
388 CELLS INFECTED WITH PURIFIED B PARTICLES FROM RIII
439 AMMARY TUMOUR VIRUS AND OF PARTICLES FOUND IN HUMAN
142 SPONSE OF C3H-AVYFB FEMALE MICE TO A LOW ONCOGENIC
323 FURTHER EVIDENCE FOR ONCORNAVIRUSES IN HUMAN
60 ESSION OF MOUSE MAMMARY TUMOR VIRAL POLYPEPTIDES IN
384 INFECTION OF
386 THE INFECTIVITY OF THE MOUSE MAMMARY TUMOR VIRUS IN
385 BRIEF COMMUNICATION: IN VITRO SUSCEPTIBILITY OF
259 TUMORS AND THEIR LYMPHOCYTE RESPONSE TO ANTIGEN AND
9 AND MOLECULAR BASIS OF MURINE MAMMARY CARCINOMA: A
113 MOUSE MAMMARY TUMOR VIRUS AS A
314 A SOLID TUMOR ANIMAL
286 SPONTANEOUS MURINE MAMMARY ADENOCARCINOMA:
20 RAL NUCLEIC ACID ASSOCIATION KINETICS: ANALYSIS OF
438 DS AND MICE AND MEN: COMMENTS ON THE USE OF ANIMAL
264 TER ETHYLENE OXIDE TREATMENT: DISTR/ INCREASE AND
245 EXPERIMENTAL CANCER IMMUNOTHERAPY:
136 NODULE BIOASSAY OF THE MOUSE MAMMARY TUMOR VIRUS:
246 S. /
244 ACTIVE SPECIFIC IMMUNOTHERAPY WITH
137 THE ROLE OF PHYSIOLOGICAL STRESS ON TUMOR INCID/
438 AND MEN: COMMENTS ON THE USE OF ANIMAL MODELS AND
21 OF VISNA, MAEDI AND RNA TUMOR VIRUSES AS STUDIED BY
100 S IN THE ABSENCE AND PRESENCE OF HORMONES: ASSAY BY
76 S GENES IN NORMAL AND INFECTED CELLS: DETECTION BY
15 S GENES IN NORMAL AND INFECTED CELLS: DETECTION BY
332 TUMORS (MEETING ABST/ PARTICLES WITH RNA OF HIGH
211 IMMUNOLOGIC STUDIES OF THE LOW
38 DETECTION OF RNA-INSTRUCTED DNA POLYMERASE AND HIGH
321 CELLS CONTAIN TRANSCRIPTASE ASSOCIATED WITH A HIGH
42 NCAPSULATING RNA-INSTRUCTED DNA POLYMERASE AND HIGH

LEUKEMIAS.
LEUKOCYTE ADHERENCE INHIBITION ASSAY IN THE MAMMARY TUMOR VIRUS
LEUKOCYTE MIGRATION INDICES. / EFFECT OF M
LEUKOCYTE MIGRATION INHIBITION IN HUMAN BREAST CANCER WITH MOUSE
LEUKOCYTE SUBPOPULATIONS IN THE INDIRECT LEUKOCYTE ADHERENCE INH
LEUKOSIS-SARCOMA VIRUSES, AND THEIR RELATIVES. / THE CELLULAR AN
LIPIDS AND PROTEINS IN TWO STRUCTURES ISOLATED FROM THE MILK OF
LIVER OF GR STRAIN MICE.
LUNG CELLS (MEETING ABSTRACT). / OBSERVATIONS ON THE I
LUNG CELLS (SFRE:CL-1) (MEETING ABSTRACT). / OBSERVATION OF INT
LUNG CELLS TO THE MOUSE MAMMARY TUMOR VIRUS. / B
LYMPHOCYTE INHIBITION BY MAMMARY TUMOR VIRUS IN PATIENTS WITH BR
LYMPHOCYTE REACTIVITY TO PURIFIED MAMMARY TUMOR VIRUS ANTIGENS.
LYMPHOCYTE RESPONSE TO ANTIGEN AND MITOGEN. / CORRELATION BETWEE
LYMPHOCYTE RESPONSE TO MAMMARY TUMOR ANTIGENS OF MAMMARY TUMOR V
LYMPHOCYTE SENSITIZATION TO SYNGENEIC TARGET CELLS.
LYMPHOCYTE STIMULATION WITH MAMMARY TUMOR VIRUS ASSOCIATED ANTIG
LYMPHOCYTE TRANSFORMATION IN VITRO TO RIII MOUSE MILK ANTIGEN AM
LYMPHOCYTES FROM NORMAL MICE. / VIRUS-DEPE
LYMPHOCYTES OF BREAST CANCER PATIENTS. (MEETING ABSTRACT).
LYMPHOID CELLS. / EXPRESSION
L1210 LEUKEMIA CELLS BY IMMUNE ELECTRON MICROSCOPY (MEETING ABST
L1210(V) GLN- MOUSE LEUKEMIA CELLS.
L1210(V) LEUKEMIA CELL LINES BY MORPHOLOGICAL, VIROLOGICAL, AND
MACROPHAGE MIGRATION INHIBITION AND LYMPHOCYTE STIMULATION WITH
MAGNETIC RESONANCE RELAXATION TIMES IN TISSUES OF TUMOR-BEARING
MASTOPATHY WITH MURINE MAMMARY CARCINOMAS: LOCATION OF THE ANTI
MASTOPATHY. / STRUCTURAL, ANTIGE
MCF-7. / REPLICATION OF ONCORNAVIRUS
MCF-7. / HORMONAL STIMULATION OF A VIRUS-REL
MEMBRANE OF INFECTED MOUSE SPLEEN CELLS.
MEMBRANE OF MILK GLOBULES. / STUDY OF THE COMPOSITION OF LIPIDS
MEMBRANES OF LYMPHOID CELLS.
METHANOL EXTRACTION RESIDUE OF BCG AND PREVENTION OF ACCELERATIO
METHANOL-EXTRACTION RESIDUE (MER) FRACTION OF BCG: SOLID TUMORS.
MICROFILAMENT POLYMERIZATION AND VIRUS PRODUCTION (MEETING ABSTR
MILK (MEETING ABSTRACT). / CHARACTERIZAT
MILK ANTIGEN AMONG WOMEN WITH BREAST DISEASE.
MILK BY HYBRIDIZATION TO POLYADENYLIC ACID SEQUENCES. / QUANTITA
MILK GLOBULES. / STUDY OF THE COMPOSITION OF LIPIDS AND PROTEIN
MILK OF INFECTED MICE: MAMMARY TUMOR VIRUS AND THE MEMBRANE OF M
MILK ON THE MOUSE MAMMARY TUMOR VIRUS.
MILK PARTICULATES. / CATION PREFERENCES FOR POLY(RC).OLIGO(DG)-D
MILK SAMPLES AND HUMAN BREAST TISSUE ON HUMAN LEUKOCYTE MIGRATIO
MILK SOURCE ON TRANSPLANTABILITY OF HISTOCOMPATIBLE MAMMARY TUMO
MILK. / DETECTION O
MILK. / IMMUNOLOGICAL RELATIONSHIPS BETWEEN MUMTV,
MILK. / DETECTION OF MOUSE MAMMARY TUMOR VIRUS IN CAT KIDNEY
MILK. (PP. 377-388) / PROPERTIES OF THE MOUSE M
MILK-BORNE MAMMARY TUMOR VIRUS. / RE
MILK: THE PRODUCTION OF CORES (MEETING ABSTRACT).
MILKS AND TISSUES. / EXPR
MINK EMBRYONIC CELLS WITH THE MOUSE MAMMARY TUMOR VIRUS.
MINK LUNG CELLS (MEETING ABSTRACT). / OBSERVATIONS ON
MINK LUNG CELLS TO THE MOUSE MAMMARY TUMOR VIRUS.
MITOGEN. / CORRELATION BETWEEN THE CLINICAL STATUS OF MICE BEARI
MODEL FOR HUMAN BREAST CANCER. / A COMPARATIVE STUDY OF THE BIOL
MODEL FOR VIRAL CARCINOGENESIS.
MODEL PREDICTIVE FOR HUMAN BREAST CANCER.
MODEL SYSTEM FOR EVALUATION OF COMBINED METHODS OF THERAPY.
MODEL SYSTEMS AND NATURAL TISSUES. / PRIMATE AND MURINE TYPE-C V
MODELS AND MOLECULAR HYBRIDIZATION IN THE SEARCH FOR HUMAN TUMOR
MODIFICATION OF THE CARCINOGENIC POWER OF MAMMARY TUMOR VIRUS AF
MODIFICATION OF TUMOR CELLS TO INCREASE IMMUNOGENICITY.
MODIFICATIONS AND QUANTITATIVE CONSIDERATIONS.
MODIFIED TUMOR CELLS IN THE IMMUNOTHERAPY OF SOLID MAMMARY TUMOR
MODIFIED TUMOR CELLS.
MODIFYING EFFECTS OF A BENIGN VIRUS ON THE MALIGNANT PROCESS AND
MOLECULAR HYBRIDIZATION IN THE SEARCH FOR HUMAN TUMOR VIRUSES.
MOLECULAR HYBRIDIZATION. / THE RELATIONSHIP
MOLECULAR HYBRIDIZATION. / PRODUCTION OF MOUSE MAMMARY TUMOR VIR
MOLECULAR HYBRIDIZATION. / THE PRESENCE AND EXPRESSION OF RNA TU
MOLECULAR HYBRIDIZATION. / THE PRESENCE AND EXPRESSION OF RNA TU
MOLECULAR WEIGHT AND RNA-DIRECTED DNA POLYMERASE IN HUMAN BRAIN
MOLECULAR WEIGHT DNA BINDING PROTEIN OF MURINE ONCORNAVIRUSES.
MOLECULAR WEIGHT RNA IN MALIGNANT TISSUE (MEETING ABSTRACT).
MOLECULAR WEIGHT VIRUS-RELATED RNA. / HUMAN LEUKAEMIC
MOLECULAR WEIGHT VIRUS-RELATED RNA IN HERPESVIRUS INDUCED TUMOUR

402 RNAVIRUS-LIKE PARTICLES PRODUCED IN MURINE MOPC-460
503 PRENEOPLASTIC, AND NEOPLASTIC MOUSE MAMMARY TISS/
247 NEOUS MAMMARY CARCINOMAS USING DIRECT INJECTIONS OF
253 ATE ANTIGENS OF MAMMARY C/ DIFFERENTIAL EFFECT OF
136 AND QUANTITATIVE CONSIDERATIONS./
374 TURE./ PROLIFERATION OF PRENEOPLASTIC MAMMARY
302 SERIAL TRANSPLANTATION OF URETHAN-TREATED MAMMARY
129 MULATION ON THE TUMOR-PRODUCING CAPABILITIES OF THE
305 AND ESTRADIOL RECEPTORS IN THE D SERIES OF MAMMARY
130 APPEARANCE OF VIRUS PARTICLES IN BALB/C MAMMARY
297 R-PRODUCING CAPABILITIES OF SERIES D BALB/C MAMMARY
37 YMERASE ACTIVITY AND DNA SYNTHESIS IN PRENEOPLASTIC
298 ARCINOGEN-INDUCED MAMMARY TUMORS FROM PRENEOPLASTIC
306 ARCINOGEN-INDUCED MAMMARY TUMORS FROM PRENEOPLASTIC
293 ATTEMPTS TO DETECT
129 FECTS OF 3-METHYLCHOLANTHRENE, MAMMARY TUMOR VIRUS,
373 SUSPECTED PRENEOPLASTIC NATURE OF MAMMARY
143 PRENEOPLASTIC SIGNIFICANCE OF HYPERPLASTIC ALVEOLAR
36 RNA-DEPENDENT DNA POLYMERASE IN PRENEOPLASTIC
169 MAMMARY TUMORS, PLAQUES, AND HYPERPLASTIC ALVEOLAR
103 MOR-PRODUCING CAPABILITIES OF HYPERPLASTIC ALVEOLAR
375 / CHEMICAL CARCINOGEN-INDUCED HYPERPLASTIC
20 D NATURAL TISSUE/ PRIMATE AND MURINE TYPE-C VIRAL
12 CE MICROSCOPY./ IDENTIFICATION OF THE
1 ELECTRON MICROSCOPY OF THE
8 S./ RELATIONSHIP IN
22 (ONCORNAVIRUSES)./ HELICAL
398 CYTOPLASMIC A PARTICLES: MOUSE MAMMARY TUMOR VIRUS
6 ./
11 MAMMARY TUMOUR VIRUS SPECIFIC
19 IBROBLASTS / PURIFICATION OF DNA COMPLEMENTARY TO
252 SE OF TUMOR BEARER AND NORMAL MOUSE SPLEEN CELLS TO
122 L CLONES./ VARIATIONS IN
170 CARCINOMA OF MICE BY TREATMENT WITH INTERFERON AND
40 ND HUMAN MILK PARTICULATE/ CATION PREFERENCES FOR
171 MAMMARY TUMORS IN C3H/HE MICE AFTER TREATMENT WITH
322 US-LIKE PARTICLES IN HUMAN MILK BY HYBRIDIZATION TO
115 Y TUMOR VIRUS PRODUCTION STIMULATED BY HORMONES AND
31 EFFECT OF LONG-TERM INCUBATION ON RNA DEPENDENT DNA
37 TGROWTH OF BALB/C AND C3H MOUSE MAMMARY GLAN/ DNA
41 MENTS (MEETING ABSTRACT)./ RNA-DEPENDENT DNA
38 EETING ABSTRACT)/ DETECTION OF RNA-INSTRUCTED DNA
42 ENCE FOR PARTICLES ENCAPSULATING RNA-INSTRUCTED DNA
333 NG ABSTR/ PARTICLES CONTAINING RNA-INSTRUCTED DNA
32 ISOLATION AND CHARACTERIZATION OF RNA-DIRECTED DNA
33 ISOLATION AND CHARACTERIZATION OF RNA-DIRECTED DNA
332 H RNA OF HIGH MOLECULAR WEIGHT AND RNA-DIRECTED DNA
35 CHARACTERIZATION AND SEPARATION OF VIRAL DNA
36 AND OF BALB/C MICE./ RNA-DEPENDENT DNA
331 PURIFICATION AND CHARACTERIZATION OF THE DNA
26 VIRAL RNA-DEPENDENT DNA
27 ON AND PROPERTIES OF MURINE MAMMARY TUMOR VIRUS DNA
28 MOR VIRUS./ RNASE H AND RNA-DIRECTED DNA
30 MOUSE MAMMARY TUMOR VIRUS DNA
34 MOUSE MAMMARY TUMOUR VIRUS RNA-DEPENDENT DNA
24 A HYBRIDS AND RNA-RNA DUPLEXES AS TEMPLATES FOR THE
51 MICROFILAMENT
162 CLASSES OF PROTEINS FOR AN RNA TUMO/ INDEPENDENT
400 MOUSE MAMMARY TUMOR VIRUS
401 IDENTIFICATION OF MOUSE MAMMARY TUMOR VIRUS (MMTV)
61 STRUCTURE OF THE MOUSE MAMMARY TUMOR VIRUS:
60 EXPRESSION OF MOUSE MAMMARY TUMOR VIRAL
56 CURSOR-PRODUCT RELATIONSHIP BETWEEN NONGLYCOSYLATED
57 ON OF TWO GROUP-SPECIFIC ANTIGENS./
58 N OF TWO MAJOR GLYCOPROTEINS WITH THE VIRAL STRU/
55 UCTURAL COMPONENTS OF MOUSE MAMMARY TUMOR VIRUS. I.
399 S ANTIGEN ON INTRACYTOPLASMIC A PARTICLE STRUCTURAL
308
145
131 THE ROLE OF
312 ON TRANSPLANTED MAMMARY TUMOR GROWTH AND PITUITARY
132 (MEETING ABSTRACT)./ UTERINE, VAGINAL, AND
294 : THE EFFECT OF TUMOR R/ PLASMA LEVELS OF A VIRAL
17 ETICS OF VIRUS PRODUCTION AND THE EFFECT OF RNA AND
211 GIC STUDIES OF THE LOW MOLECULAR WEIGHT DNA BINDING
59 IDENTIFICATION OF A PRECURSOR
48 NENTS OF THE MOUSE MAMMARY TUMOR VIRUS: II. VIRAL
162 TOR SITES FOR THE SYNTHESIS OF DIFFERENT CLASSES OF

MYELOMA CELLS. / RELATIONSHIPS BETWEEN INTRACISTERNAL TYPE A AN
NEOVASCULARIZATION INDUCED BY INTRAOCULAR XENOGRAFTS OF NORMAL,
NEURAMINIDASE AND BCG. / REGRESSION OF SPONTA
NEURAMINIDASE ON THE IMMUNOGENICITY OF VIRAL ASSOCIATED AND PRIV
NODULE BIOASSAY OF THE MOUSE MAMMARY TUMCR VIRUS: MODIFICATIONS
NODULE OUTGROWTH IN MAMMARY FAT PADS OF BALB/C MICE IN ORGAN CUL
NODULE OUTGROWTH LINE D1.
NODULE OUTGROWTH LINE D1. / COMBINED EFFECTS OF 3-METHYLCHOLANTH
NODULE OUTGROWTH LINES AND TUMORS. / HORMONE DEPENDENCE
NODULE OUTGROWTH LINES TRANSPLANTED INTO BALB/CF. C3H AND (C3HF
NODULE OUTGROWTH LINES. / EFFECTS OF VARIOUS ONCOGENIC AGENTS ON
NODULE OUTGROWTH OF BALB/C AND C3H MOUSE MAMMARY GLAND. / DNA PO
NODULE OUTGROWTHS IN BALB/C MICE. / C
NODULE OUTGROWTHS. / EFFECT OF HORMONE STIMULATION, DOSE, AND TI
NODULE-INDUCING VIRUS IN STRAIN RIII MICE.
NODULE-INDUCING VIRUS, AND PROLONGED HORMONAL STIMULATION ON THE
NODULES (HAN) DERIVED FROM ORGAN CULTURE.
NODULES (HAN) IN THE STRAIN GR MOUSE. / OCCURRENCE AND
NODULES AND TUMORS OF THE MAMMARY GLAND OF BALB/C MICE.
NODULES IN VARIOUS COMBINATIONS OF MOUSE INBRED STRAINS AND THE
NODULES IN VIRGIN AND HORMONE-STIMULATED BALB/C F. C3H AND C3HF
NODULES IN WHOLE MAMMARY GLAND ORGAN CULTURE (MEETING ABSTRACT).
NUCLEIC ACID ASSOCIATION KINETICS: ANALYSIS OF MODEL SYSTEMS AN
NUCLEIC ACID OF MOUSE MAMMARY TUMOR VIRUS (MTV) USING FLUORESCEN
NUCLEIC ACID OF MOUSE MAMMARY TUMOR VIRUS.
NUCLEIC ACID SEQUENCES BETWEEN MOUSE MAMMARY TUMOR VIRUS VARIANT
NUCLEOCAPSID STRUCTURE OF THE ONCOGENIC RIBONUCLEIC ACID VIRUSES
NUCLEOPROTEIN CORES? / INTRA
NUCLEOTIDE SEQUENCE HOMOLOGIES AMONG MOUSE MAMMARY TUMOR VIRUSES
NUCLEOTIDE SEQUENCES IN MOUSE DNA.
NUCLEOTIDE SEQUENCES REQUIRED FOR NEOPLASTIC TRANSFORMATION OF F
PHA AND SYNGENEIC TUMOR EXTRACTS IN VITRO: EFFECT OF XENOGENEIC
PHENOTYPIC EXPRESSION OF MMTV IN MOUSE MAMMARY TUMOR-DERIVED CEL
POLY I:C (MEETING ABSTRACT). / INHIBITION OF SPONTANEOUS MAMMAR
POLY(RC).OLIGO(DG)-DIRECTED DNA SYNTHESIS BY RNA TUMOR VIRUSES A
POLYADENYLATE-POLYURIDYLATE. / REDUCED INCIDENCE OR SPONTANEOUS
POLYADENYLIC ACID SEQUENCES. / QUANTITATION OF RNA TUMOR VIRUSES
POLYAMINES IN CELLS GROWN IN SEMI-SYNTHETIC IN VITRO CONDITIONS.
POLYMERASE (RDP) ACTIVITY IN MOUSE MAMMARY TUMOR VIRUS (MMTV).
POLYMERASE ACTIVITY AND DNA SYNTHESIS IN PRENEOPLASTIC NODULE OU
POLYMERASE ACTIVITY IN FIVE RNA VIRUSES: DIVALENT CATION REQUIRE
POLYMERASE AND HIGH MOLECULAR WEIGHT RNA IN MALIGNANT TISSUE (M
POLYMERASE AND HIGH MOLECULAR WEIGHT VIRUS-RELATED RNA IN HERPES
POLYMERASE AND VIRUS-RELATED RNA IN HUMAN BREAST CANCERS (MEETI
POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS (MEETING ABSTRACT).
POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS.
POLYMERASE IN HUMAN BRAIN TUMORS (MEETING ABSTRACT). / PARTICLE
POLYMERASE IN MOUSE MILK (MEETING ABSTRACT).
POLYMERASE IN PRENEOPLASTIC NODULES AND TUMORS OF THE MAMMARY GL
POLYMERASE OF HUMAN BREAST CANCER PARTICLES.
POLYMERASE.
POLYMERASE. / PURIFICATI
POLYMERASE: ASSOCIATED ENZYMATIC ACTIVITIES OF MURINE MAMMARY TU
POLYMERASE: PURIFICATION AND PROPERTIES (MEETING ABSTRACT).
POLYMERASE: REQUIREMENTS AND PRODUCTS.
POLYMERASES OF THE ONCOGENIC RNA VIRUSES. / SYNTHETIC DNA-RN
POLYMERIZATION AND VIRUS PRODUCTION (MEETING ABSTRACT).
POLYPEPTIDE CHAIN INITIATOR SITES FOR THE SYNTHESIS OF DIFFERENT
POLYPEPTIDE PRECURSORS IN INTRACYTOPLASMIC A PARTICLES.
POLYPEPTIDE PRECURSORS IN INTRACYTOPLASMIC A PARTICLES (MEETING
POLYPEPTIDES AND GLYCOPROTEINS.
POLYPEPTIDES IN MILKS AND TISSUES.
POLYPEPTIDES OF A AND B PARTICLES OF MOUSE MAMMARY TUMOR VIRUS.
POLYPEPTIDES OF THE MOUSE MAMMARY TUMOR VIRUS. I. CHARACTERIZATI
POLYPEPTIDES OF THE MOUSE MAMMARY TUMOR VIRUS. II. IDENTIFICATIO
POLYPEPTIDES OF THE VIRION. / STR
POLYPEPTIDES. (MEETING ABSTRACT). / LOCALIZATION OF MOUSE MAMMA
PREGNANCY DEPENDENCE OF MAMMARY TUMORS IN STRAIN DDD MICE.
PREGNANCY DEPENDENCE OF MAMMARY TUMORS IN STRAIN DDD MICE.
PROLACTIN IN CARCINOGENESIS. (PP. 107-136)
PROLACTIN LEVEL IN BALB/C MICE. / EFFECT OF ERGOCORNINE
PROLACTIN RESPONSES TO DIETARY DIETHYLSTILBESTROL IN THE MOUSE.
PROTEIN AS A DIAGNOSTIC SIGNAL FOR THE PRESENCE OF MAMMARY TUMOR
PROTEIN INHIBITORS ON VIRAL SYNTHESIS. / REPLICATION OF MOUSE MA
PROTEIN OF MURINE ONCORNAVIRUSES. / IMMUNOLO
PROTEIN TO THE MAJOR GLYCOPROTEINS OF MOUSE MAMMARY TUMOR VIRUS.
PROTEINS AND ANTIGENS. / CHARACTERISTICS OF THE STRUCTURAL COMPO
PROTEINS FOR AN RNA TUMOR VIRUS: MOUSE MAMMARY TUMOR VIRUS.

330 MURINE TUMOR VIRUS-LIKE
62 CE: MAMMA/ STUDY OF THE COMPOSITION OF LIPIDS AND
198 Y GLANDS IN MICE OF VAR/ EXPRESSION OF INDIVIDUAL
4 Y TUMOR VIRUS SEQUENCES NOT TRANSMITTED AS GERMINAL
393 BY ULTRACENTRIFUGATION OF THE LACTEOUS FACTOR FROM
210 PROVIDED BY MURINE MAMMARY TUMOR VIRUS./
168 CELLS AND MAMMAR/ DIFFERENTIAL EFFECT OF IONIZING
311 TARGET ORGAN FOR A SYSTEMIC EFFECT OF ULTRAVIOLET
188 THE
185 N./
187
184 PROCEDURES FOR
186 ATION OF MOUSE MAMMARY TUMOR VIRUS (MTV) VIRIONS BY
189 MURINE MAMMARY TUMOR VIRUS AND ITS QUANTITATION BY
167 FURTHER STUDIES ON THE
166 IRRADIATION./
390 MOUSE MAMMARY TUMOR VIRUS DNA IN INFECTED
389 INFECTION OF CULTURED
164 SE MAMMARY TUMOUR CELLS. ABSENCE O/ FUSION OF XC
397 SE MAMMARY TUMOUR CELLS. ABSENCE O/ FUSION OF XC
121 AND RECOVERY OF MOUSE MAMMARY TUMOR VIRUS WITH HIGH
31 G-TERM INCUBATION ON RNA DEPENDENT DNA POLYMERASE (
108 Y GLUCOCORTICOID. / RELATIONSHIP BETWEEN
305 TUMORS./ HORMONE DEPENDENCE AND ESTRADIOL
18 IBILITY OF A DNA-CONTAINING MAMMARY TUMOUR VIRUS IN
369 NDENCE OF HORMONE-INDUCED CELLULAR ORGANIZATION./
362 STABLISHMENT OF A MOUSE MAMMARY TUMOR CELL LINE./
17 KINETICS OF VIRUS PRODUCTION AND THE EFFECT OF R/
319 OMA CELL LINE, MCF-7./
174 F MICE. II. INHERENT DIFFERENCES / MECHANISM OF
173 GL MICE./ THE GENETICS OF
223 CHARACTERIZATION OF X/GF MICE WITH RESPECT TO THEIR
284 POSITIVE CORRELATION OF CHEMOTHERAPEUTIC
44 IONSHIPS./
43 SEROLOGICAL ANALYSIS OF
7 ION OF MOUSE MAMMARY TUMOR VIRUSES IN MOUSE STRAINS
141 OMMUNICATION./ BIOACTIVITY OF C3H AND
293 ATTEMPTS TO DETECT NODULE-INDUCING VIRUS IN STRAIN
388 IDNEY CELLS INFECTED WITH PURIFIED B PARTICLES FROM
368 RUS (MTV) PRODUCTION (MEETING AB/ AN ESTABLISHED
341 LYMPHOCYTE TRANSFORMATION IN VITRO TO
4 NOT TRANSMITTED AS GERMINAL PROVIRUS IN THE C3H AND
301 SPONTANEOUS KIDNEY TUMORS IN A SUBSTRAIN OF
147 CE OF A, B, AND C VIRUS-LIKE PARTICLES IN ORGANS OF
318 HOMOLOGY BETWEEN HUMAN BREAST TUMOUR
17 II. KINETICS OF VIRUS PRODUCTION AND THE EFFECT OF
31 OR VIRUS (MMTV/ EFFECT OF LONG-TERM INCUBATION ON
3 VISUALIZATION OF THE GENOMIC
25 SOLATES AND OTHER ONCORNAVIRU/ MASON-PFIZER VIRUS
320 PRESENCE IN HUMAN BREAST CANCER OF
10 EVIDENCE FOR TRANSLATION OF VIRAL-SPECIFIC
42 POLYMERASE AND HIGH MOLECULAR WEIGHT VIRUS-RELATED
333 ING RNA-INSTRUCTED DNA POLYMERASE AND VIRUS-RELATED
317 MOUSE MAMMARY TUMOR VIRUS RELATED
38 INSTRUCTED DNA POLYMERASE AND HIGH MOLECULAR WEIGHT
325 DETECTION OF HIGH-MOLECULAR-WEIGHT
39 ROM MAMMARY TUMOR/ VIRION-ASSOCIATED AND CELLULAR
332 HUMAN BRAIN TUMORS (MEETING ABST/ PARTICLES WITH
25 MASON-PFIZER VIRUS RNA GENOME: RELATIONSHIP TO THE
13 MMARY TUMOR VIRUS./ ANALYSIS OF THE TRANSFER
5 NS OF MOUSE MAMMARY TUMOR VIRUS AS SHOWN BY PARTIAL
320 CER OF RNA HOMOLOGOUS TO MOUSE MAMMARY TUMOUR VIRUS
105 RUS: EFFECT UPON SYNTHESIS AND DEGRADATION OF VIRAL
321 SOCIATED WITH A HIGH MOLECULAR WEIGHT VIRUS-RELATED
104 MOR VIRUS RNA: INCREASED RATE OF SYNTHESIS OF VIRAL
41 ENT CATION REQUIREMENTS (MEETING ABSTRACT)./
36 OF THE MAMMARY GLAND OF BALB/C MICE./
26 VIRAL
34 MOUSE MAMMARY TUMOUR VIRUS
33 ISOLATION AND CHARACTERIZATION OF
32 NG ABSTRACT). / ISOLATION AND CHARACTERIZATION OF
332 PARTICLES WITH RNA OF HIGH MOLECULAR WEIGHT AND
28 MURINE MAMMARY TUMOR VIRUS./ RNASE H AND
42 LATED RN/ NO EVIDENCE FOR PARTICLES ENCAPSULATING
333 AST CANCERS (MEETING ABSTR/ PARTICLES CONTAINING
38 ALIGNANT TISSUE (MEETING ABSTRACT)/ DETECTION OF
24 IC RNA VIRUSES./ SYNTHETIC DNA-RNA HYBRIDS AND
104 TIMULATED ACCUMULATION OF MOUSE MAMMARY TUMOR VIRUS

PROTEINS IN HUMAN BREAST CANCERS (MEETING ABSTRACT).
PROTEINS IN TWO STRUCTURES ISOLATED FROM THE MILK OF INFECTED MI
PROTEINS OF MOUSE MAMMARY GLAND CANCER VIRUS IN TUMORS OF MAMMAR
PROVIRUS IN THE C3H AND RIII MOUSE STRAINS. / ISOLATION OF THE M
PS STRAIN MICE PERFORMED ON FICOLL GRADIENTS. / BIOLOGICAL ACTIV
PSEUDOTYPES OF VESICULAR STOMATITIS VIRUS WITH ENVELOPE ANTIGENS
RADIATION ON MAMMARY TUMOR VIRUS ACTIVITY ASSOCIATED WITH BLOOD
RADIATION.
RADIOIMMUNOASSAY (RIA).
RADIOIMMUNOASSAY FOR MOUSE MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGE
RADIOIMMUNOASSAY FOR MTV-ANTIGENS.
RADIOIMMUNOASSAY OF THE MOUSE MAMMARY TUMOR VIRUS.
RADIOIMMUNOASSAY. / QUANTIT
RADIOIMMUNOASSAY. / THE PURIFICATION OF A GS ANTIGEN OF THE
RADIORESISTANCE OF HIGHLY PURIFIED MOUSE MAMMARY TUMOR VIRUS.
RADIORESISTANCE OF VIRUS FROM MURINE MAMMARY TUMORS AFTER GAMMA
RAT CELLS: CHARACTERIZATION OF UNINTEGRATED FORMS.
RAT HEPATOMA CELLS BY MOUSE MAMMARY TUMOR VIRUS.
RAT SARCOMA CELLS INDUCED BY MURINE LEUKAEMIA VIRUS-INFECTED MOU
RAT SARCOMA CELLS INDUCED BY MURINE LEUKAEMIA VIRUS-INFECTED MOU
RDDP ACTIVITY. / OPTIMIZATION OF DEXAMETHASONE-STIMULATED MMSMT
RDP) ACTIVITY IN MOUSE MAMMARY TUMOR VIRUS (MMTV). / EFFECT OF L
RECEPTOR AND MAMMARY TUMOUR VIRUS PRODUCTION AFTER STIMULATION B
RECEPTORS IN THE D SERIES OF MAMMARY NODULE OUTGROWTH LINES AND
RED BLOOD CELLS OF MOUSE. / POSS
REPLICATION OF MAMMARY TUMOR VIRUS IN TUMOR CELL CULTURES: DEPE
REPLICATION OF MOUSE MAMMARY TUMOR VIRUS IN TISSUE CULTURE. I. E
REPLICATION OF MOUSE MAMMARY TUMOR VIRUS IN TISSUE CULTURE. II.
REPLICATION OF ONCORNAVIRUS-LIKE PARTICLE IN HUMAN BREAST CARCIN
RESISTANCE TO MAMMARY TUMOR DEVELOPMENT IN C57BL AND I STRAINS O
RESISTANCE TO MAMMARY TUMOR VIRUS (MTV-S) IN C57BL/CRGL AND I/CR
RESISTANCE TO ONCOGENESIS. /
RESULTS IN HUMAN AND MURINE SOLID CARCINOMA.
REVERSE TRANSCRIPTASE OF RNA TUMOR VIRUSES: IMMUNOLOGICAL RELAT
REVERSE TRANSCRIPTASE OF THE MASON-PFIZER MONKEY VIRUS.
RIII AND C3H. / A BIOCHEMICAL APPROACH TO THE STUDY OF THE TRANS
RIII MAMMARY TUMOR VIRUSES IN VIRGIN FEMALE BALB/C MICE: BRIEF C
RIII MICE.
RIII MILK. / DETECTION OF MOUSE MAMMARY TUMOR VIRUS IN CAT K
RIII MOUSE MAMMARY TUMOR CELL LINE: KINETICS OF MAMMARY TUMOR VI
RIII MOUSE MILK ANTIGEN AMONG WOMEN WITH BREAST DISEASE.
RIII MOUSE STRAINS. / ISOLATION OF THE MOUSE MAMMARY TUMOR VIRUS
RIII/DM/SE MICE.
RIII/DM/SE MICE. / PRESEN
RNA AND MOUSE MAMMARY TUMOUR VIRUS GENOME.
RNA AND PROTEIN INHIBITORS ON VIRAL SYNTHESIS. / REPLICATION OF
RNA DEPENDENT DNA POLYMERASE (RDP) ACTIVITY IN MOUSE MAMMARY TUM
RNA FROM A B-TYPE TUMOR VIRUS (MEETING ABSTRACT).
RNA GENOME: RELATIONSHIP TO THE RNA OF MORPHOLOGICALLY SIMILAR I
RNA HOMOLOGOUS TO MOUSE MAMMARY TUMOUR VIRUS RNA.
RNA IN CELLS OF A MOUSE MAMMARY CARCINOMA (MEETING ABSTRACT).
RNA IN HERPESVIRUS INDUCED TUMOURS OF NON-HUMAN PRIMATES. / NO E
RNA IN HUMAN BREAST CANCERS (MEETING ABSTRACT). / PARTICLES CON
RNA IN HUMAN TUMORS (MEETING ABSTRACT).
RNA IN MALIGNANT TISSUE (MEETING ABSTRACT). / DETECTION OF RNA@
RNA IN PARTICLES FROM HUMAN MILK.
RNA METHYLASE ACTIVITY IN NORMAL AND NEOPLASTIC MAMMARY TISSUE F
RNA OF HIGH MOLECULAR WEIGHT AND RNA-DIRECTED DNA POLYMERASE IN
RNA OF MORPHOLOGICALLY SIMILAR ISOLATES AND OTHER ONCORNAVIRUSES
RNA POPULATION OF MOUSE MAMMARY GLANDS INFECTED WITH A LATENT MA
RNA SEQUENCE ANALYSIS. / DIFFERENCES BETWEEN GENOMES OF TWO STR
RNA. / PRESENCE IN HUMAN BREAST CAN
RNA. / STEROID INDUCTION OF MOUSE MAMMARY TUMOR VI
RNA. / HUMAN LEUKAEMIC CELLS CONTAIN TRANSCRIPTASE AS
RNA. / GLUCOCORTICOID-STIMULATED ACCUMULATION OF MOUSE MAMMARY T
RNA-DEPENDENT DNA POLYMERASE ACTIVITY IN FIVE RNA VIRUSES: DIVAL
RNA-DEPENDENT DNA POLYMERASE IN PRENEOPLASTIC NODULES AND TUMORS
RNA-DEPENDENT DNA POLYMERASE.
RNA-DEPENDENT DNA POLYMERASE: REQUIREMENTS AND PRODUCTS.
RNA-DIRECTED DNA POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS.
RNA-DIRECTED DNA POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS (MEETI
RNA-DIRECTED DNA POLYMERASE IN HUMAN BRAIN TUMORS (MEETING ABST
RNA-DIRECTED DNA POLYMERASE: ASSOCIATED ENZYMATIC ACTIVITIES OF
RNA-INSTRUCTED DNA POLYMERASE AND HIGH MOLECULAR WEIGHT VIRUS-RE
RNA-INSTRUCTED DNA POLYMERASE AND VIRUS-RELATED RNA IN HUMAN BRE
RNA-INSTRUCTED DNA POLYMERASE AND HIGH MOLECULAR WEIGHT RNA IN M
RNA-RNA DUPLEXES AS TEMPLATES FOR THE POLYMERASES OF THE ONCOGEN
RNA: INCREASED RATE OF SYNTHESIS OF VIRAL RNA. / GLUCOCORTICOID-

28 TIVITIES OF MURINE MAMMARY TUMOR VIRUS./
96 ECTRON MICROSCOPY FOR MURINE MAMMARY TUMOR (MUMTV),
98 LASER / HYDRODYNAMIC DIAMETERS OF MURINE MAMMARY,
96 PY FOR MURINE MAMMARY TUMOR (MUMTV), ROUS SARCOMA (
255 NGENEIC HOSTS AGAINST TUMOR CELL SURFACE INCOMPLETE
96 N MICROSCOPY FOR MURINE MAMMARY TUMOR (MUMTV), ROUS
164 AMMARY TUMOUR CELLS. ABSENCE O/ FUSION OF XC RAT
397 AMMARY TUMOUR CELLS. ABSENCE O/ FUSION OF XC RAT
19 R NEOPLASTIC TRANSFORMATION OF FIBROBLASTS BY AVIAN
98 HYDRODYNAMIC DIAMETERS OF MURINE MAMMARY, ROUS
370 IC MAMMARY EPITHELIAL CELLS IN VITRO: COMPARISON OF
377 BUDDING FROM C3H MOUSE MAMMARY TUMOR CELLS IMMUN/
118 RNAVIRUS-PRODUCING MOUSE MAMMARY TUMOR CELL LINE BY
372 "DOMES", PERIODICALLY EXPANDING AND COLLAPSING
153 OM STRAINS C57BL AND GR: BREEDING TEST OF BACKCROSS
208 IN VITRO LYMPHOCYTE
35 ACT)./ CHARACTERIZATION AND
5 F MOUSE MAMMARY TUMOR VIRUS AS SHOWN BY PARTIAL RNA
6 NUCLEOTIDE
8 RELATIONSHIP IN NUCLEIC ACID
14 MARY EPITHELIAL CELLS OF THE BALB/ LEVELS OF MMTV
11 MAMMARY TUMOUR VIRUS SPECIFIC NUCLEOTIDE
4 II MO/ ISOLATION OF THE MOUSE MAMMARY TUMOR VIRUS
19 PURIFICATION OF DNA COMPLEMENTARY TO NUCLEOTIDE
322 IN HUMAN MILK BY HYBRIDIZATION TO POLYADENYLIC ACID
252 RACTS IN VITRO: EFFECT OF XENOGENEIC AND SYNGENEIC
228 LS. / COMPLEXITY OF FACTORS IN
227 TOWARD THE AUTOLOGOUS TUMOR. / ANTIBODY IN THE
348 NEUTRALIZATION OF MURINE MAMMARY TUMOR VIRUS BY
347 AN ANTIGEN IN HUMAN BREAST CANCER
302 TH LINE D1./
297 ONCOGENIC AGENTS ON TUMOR-PRODUCING CAPABILITIES OF
305 HORMONE DEPENDENCE AND ESTRADIOL RECEPTORS IN THE D
43 R MONKEY VIRUS./
230 ACTIVITY IN VITRO DETECTED BY DIFFERENT METHODS OF
230 F SPLEEN CELL ACTIVITY IN VITRO DETECTED BY DIFF/
340 ANTIBODY REACTING WITH MOUSE MAMMARY TUMOR VIRUS IN
376 ES AND PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS IN A
403 ON C-TYPE PARTICLE INFECTED CHIMPANZEE LUNG CELLS (
213 CITES LEUKEMIA / ANTIBODY-INDUCED MODULATION AND
148 Y TUMORIGENESIS: ESTABLISHMENT OF TWO NEW STRAINS (
66 NE LEUKEMIA VIRUS, AND MASON-PFIZER MONKEY VIRUS/
148 IGENESIS: ESTABLISHMENT OF TWO NEW STRAINS (SHN AND
242 F BCG AND PREVENTION OF ACCELERATION BY CONCOMITANT
243 227-244)/ ACTIVE
244 ACTIVE
11 MAMMARY TUMOUR VIRUS
258 UMORS IN MICE (MEETING ABSTRACT)./ EFFECT OF
199 STRAIN
354 IONS: FORMAL DISCUSSION. /
349 CLES OF THE MURINE MAMMARY TUMOR VIRUS. /
96 BETWEEN DIAMETERS MEASURED BY LASER BEAT FREQUENCY
98 S: STUDIES BY LASER BEAT FREQUENCY LIGHT-SCATTERING
229 ANTIGENS./ BLOCKING OF
230 IN MAMMARY NEOPLASIA: ENHANCEMENT AND ANTAGONISM OF
227 ODY IN THE SERA OF TUMOR-BEARING MICE THAT MEDIATES
231 ESPONSES TO MTV-INDUCED MAMMARY TUMORS: ACTIVITY OF
252 FERENTIAL RESPONSE OF TUMOR BEARER AND NORMAL MOUSE
271 SOCIATED ANTIGENS ON THE MEMBRANE OF INFECTED MOUSE
234 IS BY MAMMARY TUMOR VIRUS IN THE ABSENCE OF THYMUS,
235 MAMMARY TUMORIGENESIS IN
225 ARY TUMORS (MEETING ABSTRACT)/ IDENTIFICATION OF
216 IRION IN CBA/BLN MICE INFECTED NEONATALLY WITH T/
409 AN ELECTRON MICROSCOPIC STUDY OF
301
170 ON AND POLY I:C (MEETING ABSTRACT/ INHIBITION OF
287 INHIBITION OF
263 RY TUMOR VIRUS-CONTAINING TISSUES / IMMUNOLOGY OF
247 INIDASE AND BCG./ REGRESSION OF
282 UNUSUALLY HIGH INCIDENCE OF
171 OLYADENYLATE-POLYURIDYLATE./ REDUCED INCIDENCE OR
278 ANTIGENS: EFFECT OF IMMUNIZATION ON DEVELOPMENT OF
285 F IMMUNOSUPPRESSION ON THE GROWTH OF TRANSPLANTS OF
286 UATION OF COMBINED METHODS OF THERAPY./
222 Y TUMOR VIRUS IN MICE./
283 ACTINOMYCIN D AND X-RADIATION SUPPRESSION OF
309 MUNIZING PROPERTIES OF C3H MOUSE CELLS UNDERGOING "
219 PARTICLES (IAP) / IMMUNOFLUORESCENT DETECTION OF

RNASE H AND RNA-DIRECTED DNA POLYMERASE: ASSOCIATED ENZYMATIC AC
ROUS SARCOMA (RSV), AND FELINE LEUKEMIA (FELV) VIRUSES (MEETING
ROUS SARCOMA, AND FELINE LEUKEMIA RNA TUMOR VIRUSES: STUDIES BY
RSV), AND FELINE LEUKEMIA (FELV) VIRUSES (MEETING ABSTRACT).
SACCHARIDE MOIETIES. / HUMORAL REACTIONS IN SY
SARCOMA (RSV), AND FELINE LEUKEMIA (FELV) VIRUSES (MEETING ABSTR
SARCOMA CELLS INDUCED BY MURINE LEUKAEMIA VIRUS-INFECTED MOUSE M
SARCOMA CELLS INDUCED BY MURINE LEUKAEMIA VIRUS-INFECTED MOUSE M
SARCOMA VIRUSES. / PURIFICATION OF DNA COMPLEMENTARY TO NUCLEOT
SARCOMA, AND FELINE LEUKEMIA RNA TUMOR VIRUSES: STUDIES BY LASER
SATURATION DENSITY, MORPHOLOGY AND CONCANAVALIN A REACTIVITY.
SCANNING ELECTRON MICROSCOPY (SEM) OF MAMMARY TUMOR VIRUS (MTV)
SCANNING ELECTRON MICROSCOPY. / SURFACE LOCALIZATION OF VIRUS PR
SECRETORY STRUCTURES IN CELL CULTURES OF MOUSE MAMMARY TUMORS.
SEGREGANTS. / MOUSE MAMMARY TUMOR VIRUS IN HYBRIDS FR
SENSITIZATION TO SYNGENEIC TARGET CELLS.
SEPARATION OF VIRAL DNA POLYMERASE IN MOUSE MILK (MEETING ABSTR
SEQUENCE ANALYSIS. / DIFFERENCES BETWEEN GENOMES OF TWO STRAINS
SEQUENCE HOMOLOGIES AMONG MOUSE MAMMARY TUMOR VIRUSES.
SEQUENCES BETWEEN MOUSE MAMMARY TUMOR VIRUS VARIANTS.
SEQUENCES IN DNA OF VIRUS- AND HORMONE-INDUCED MALIGNANT MAM
SEQUENCES IN MOUSE DNA.
SEQUENCES NOT TRANSMITTED AS GERMINAL PROVIRUS IN THE C3H AND RI
SEQUENCES REQUIRED FOR NEOPLASTIC TRANSFORMATION OF FIBROBLASTS
SEQUENCES. / QUANTITATION OF RNA TUMOR VIRUSES AND VIRUS-LIKE PA
SERA (MEETING ABSTRACT). / DIFFERENTIAL RESPONSE OF TUMOR BEARE
SERA OF DIFFERENT MICE THAT AFFECT MTV-INDUCED MAMMARY TUMOR CEL
SERA OF TUMOR-BEARING MICE THAT MEDIATES SPLEEN CELL CYTOXICITY
SERA OF WOMEN WITH BREAST CANCER.
SERA RELATED TO THE MURINE MAMMARY TUMOUR VIRUS.
SERIAL TRANSPLANTATION OF URETHAN-TREATED MAMMARY NODULE OUTGROW
SERIES D BALB/C MAMMARY NODULE OUTGROWTH LINES. / EFFECTS OF VAR
SERIES OF MAMMARY NODULE OUTGROWTH LINES AND TUMORS. /
SEROLOGICAL ANALYSIS OF REVERSE TRANSCRIPTASE OF THE MASON-PFIZE
SERUM FACTOR ASSAY. / SERUM FACTORS IN MAMMARY NEOPLASIA: ENHANC
SERUM FACTORS IN MAMMARY NEOPLASIA: ENHANCEMENT AND ANTAGONISM O
SERUM OF BREAST CARCINOMA PATIENTS. /
SERUM-FREE MEDIUM. / PROPAGATION OF MOUSE MAMMARY TUMOR CELL LIN
SFRE:CL-1) (MEETING ABSTRACT). / OBSERVATION OF INTRACYTOPLASMI
SHEDDING OF MAMMARY TUMOR VIRUS ANTIGENS ON THE SURFACES OF GR A
SHN AND SLN). / TWO-WAY SELECTION OF A STOCK OF SWISS ALBINO MIC
SIALYLATION OF GLYCOPROTEINS OF MURINE MAMMARY TUMOR VIRUS, MURI
SLN). / TWO-WAY SELECTION OF A STOCK OF SWISS ALBINO MICE FOR MA
SPECIFIC IMMUNIZATION. / ACCELERATED DEVELOPMENT OF TRANSPLANTED
SPECIFIC IMMUNOTHERAPY OF CANCER IN EXPERIMENTAL ANIMALS. (PP.
SPECIFIC IMMUNOTHERAPY WITH MODIFIED TUMOR CELLS.
SPECIFIC NUCLEOTIDE SEQUENCES IN MOUSE DNA.
SPECIFIC SOLUBLE TUMOR ANTIGENS ON IMMUNE RESPONSES TO MAMMARY T
SPECIFICITY IN MOUSE MAMMARY TUMOR VIRUS VIRION ANTIGENS.
SPECIFICITY OF CELL-MEDIATED IMMUNITY IN MOUSE-HUMAN CROSS-REACT
SPECIFICITY OF HUMAN ANTIBODIES TO INTRACYTOPLASMIC TYPE-A PARTI
SPECTROSCOPY (LBFS) AND BY ELECTRON MICROSCOPY FOR MURINE MAMMAR
SPECTROSCOPY AND ELECTRON MICROSCOPY. / HYDRODYNAMIC DIAMETERS O
SPLEEN CELL ACTIVITY AGAINST TARGET MAMMARY TUMOR CELLS BY VIRAL
SPLEEN CELL ACTIVITY IN VITRO DETECTED BY DIFFERENT METHODS OF S
SPLEEN CELL CYTOXICITY TOWARD THE AUTOLOGOUS TUMOR. / ANTIB
SPLEEN CELL PREPARATIONS FROM BOTH MTV-FREE AND MTV-INFECTED MIC
SPLEEN CELLS TO PHA AND SYNGENEIC TUMOR EXTRACTS IN VITRO: EFFE
SPLEEN CELLS. / MAMMARY TUMOR VIRUS AS
SPLEEN OR BOTH ORGANS. / MOUSE MAMMARY TUMORIGENES
SPLENECTOMIZED MICE.
SPLENIC SUPPRESSOR CELL ACTIVITY IN MICE WITH MUMTV-INDUCED MAMM
SPONTANEOUS AGE-DEPENDENT PRODUCTION OF ANTIBODIES AGAINST THE V
SPONTANEOUS AND EXPERIMENTALLY INDUCED LEUKEMIA IN ICRC MICE.
SPONTANEOUS KIDNEY TUMORS IN A SUBSTRAIN OF RIII/DM/SE MICE.
SPONTANEOUS MAMMARY CARCINOMA OF MICE BY TREATMENT WITH INTERFER
SPONTANEOUS MAMMARY CARCINOMA OF MICE BY TREATMENT WITH
SPONTANEOUS MAMMARY CARCINOMAS IN MICE: IMMUNOGENICITY OF MAMMA
SPONTANEOUS MAMMARY CARCINOMAS USING DIRECT INJECTIONS OF NEURAM
SPONTANEOUS MAMMARY CARCINOMATA IN A COLONY OF BALB/C MICE.
SPONTANEOUS MAMMARY TUMORS IN C3H/HE MICE AFTER TREATMENT WITH P
SPONTANEOUS MAMMARY TUMORS. / SEARCH FOR CROSS-REACTING ANTIGENI
SPONTANEOUS MAMMARY TUMOURS IN MICE. (NEONATAL OR ADULT THYMECTO
SPONTANEOUS MURINE MAMMARY ADENOCARCINOMA: MODEL SYSTEM FOR EVAL
SPONTANEOUS OCCURRENCE OF PRECIPITATING ANTIBODIES TO THE MAMMAR
SPONTANEOUS TUMORIGENESIS IN MICE.
SPONTANEOUS" MALIGNANT CONVERSION IN VITRO. / TUMORIGENICITY AND
SPONTANEOUSLY OCCURRING ANTIBODIES IN MICE TO INTRACYTOPLASMIC A

135 IN MICE./ LONG-TERM EFFECTS OF NEONATAL
102 OR OPTIMAL MTV SYNTHESIS IN VITRO AND THE EFFECT OF
105 HESIS AND DEGRADATION OF VIRAL RNA./
236 T OF THYMECTOMY ON MAMMARY TUMORIGENESIS./ MOUSE
80 RY TUMOR VIRUS DETECTION IN MURINE BREAST CANCER OF
292 RS TRANSMITTED BY EITHER PARENT./
145 PREGNANCY DEPENDENCE OF MAMMARY TUMORS IN
308 PREGNANCY DEPENDENCE OF MAMMARY TUMORS IN
300 MAMMARY TUMOR VIRUS IN
143 CANCE OF HYPERPLASTIC ALVEOLAR NODULES (HAN) IN THE
393 ULTRACENTRIFUGATION OF THE LACTEOUS FACTOR FROM PS
99 MMARY-TUMOR VIRUS ACTIVITY IN BRAIN AND LIVER OF GR
81 PARTICLES./ FIVE-YEAR ANALYSIS OF A
293 ATTEMPTS TO DETECT NODULE-INDUCING VIRUS IN
199
178 : A NEW HIGH MAMMARY-TUMOR AND HIGH LEUKEMIA MOUSE
175 SMISSION OF THE MAMMARY TUMOR VIRUS BY THE GR MOUSE
165 THAN AND X-RAY EFFECTS ON MICE OF A TUMOR-RESISTANT
148 FOR MAMMARY TUMORIGENESIS: ESTABLISHMENT OF TWO NEW
169 LAR NODULES IN VARIOUS COMBINATIONS OF MOUSE INBRED
299 MAMMARY TUMORS IN
153 MOUSE MAMMARY TUMOR VIRUS IN HYBRIDS FROM
212 NOUS IMMUNITY TO MOUSE MAMMARY TUMOR VIRUS IN MOUSE
69 RIANTS OF MOUSE MAMMARY TUMOUR VIRUS IN HIGH TUMOUR
174 ISTANCE TO MAMMARY TUMOR DEVELOPMENT IN C57BL AND I
201 NICITY OF MAMMARY TUMOR VIRUS OBTAINED FROM SEVERAL
5 UENCE ANALYSI/ DIFFERENCES BETWEEN GENOMES OF TWO
7 RANSMISSION OF MOUSE MAMMARY TUMOR VIRUSES IN MOUSE
77 IOUS MOUSE MAMMARY TUMOR VIRUSES IN DIFFERENT MOUSE
[illegible] IRUS IN TUMORS OF MAMMARY GLANDS IN MICE OF VARIOUS
203 D WITH THE MAMMARY TUMOR VIRUS FROM DIFFERENT MOUSE
202 URES DERIVED FROM MAMMARY TUMORS OF MICE OF SEVERAL
4 TTED AS GERMINAL PROVIRUS IN THE C3H AND RIII MOUSE
174 OF MICE. II. INHERENT DIFFERENCES BETWEEN THE TWO
200 EN MOUSE MAMMARY TUMOR VIRUSES FROM DIFFERENT MOUSE
296 INHIBITION OF GROWTH OF MOUSE MAMMARY CARCINOMA BY
140 THE ROLE OF PHYSIOLOGICAL
137 THE MALIGNANT PROCESS AND THE ROLE OF PHYSIOLOGICAL
139 RS: ALTERATION OF INCIDENCE AS APPARENT FUNCTION OF
138 OF
67 IED BY LACTOPEROXIDASE IODINATION (MEETING ABST/
55 DES OF THE VIRION./
48 RAL PROTEINS AND ANTIGENS/ CHARACTERISTICS OF THE
47 PHOLOGICAL AND BIOCHEMICA/ CHARACTERISTICS OF THE
399 TUMOR VIRUS ANTIGEN ON INTRACYTOPLASMIC A PARTICLE
365 FROM PRIMARY TUMOR CELL CULTURES I: IMMUNOLOGIC AND
356 EROUS MASTOPATHY./
86 MMARY TUMOR VIRUS (MTV). EXPERIMENTAL STUDY OF THE
85 SURFACE
196 ANTIGENIC
61 YCOPROTEINS./
88 TERIZATION OF THE CORE./ THE
22 SES)./ HELICAL NUCLEOCAPSID
84 ELLS / SURFACE
58 IFICATION OF TWO MAJOR GLYCOPROTEINS WITH THE VIRAL
81 OF A STRAIN OF MAMMARY ADENOCARCINOMA: MALIGNANCY,
372 S", PERIODICALLY EXPANDING AND COLLAPSING SECRETORY
62 DY OF THE COMPOSITION OF LIPIDS AND PROTEINS IN TWO
190 SAY IN THE MAMMARY TUMOR V/ THE ROLE OF LEUKOCYTE
301 SPONTANEOUS KIDNEY TUMORS IN A
149 MAMMARY GLAND TUMORS IN
117 ION OF MOUSE MAMMARY TUMOR VIRUS (MEETING ABSTR/
283 ACTINOMYCIN D AND X-RADIATION
225 RS (MEETING ABSTRACT)/ IDENTIFICATION OF SPLENIC
237 THE ROLE OF T AND
254 ELLS INDUCING HUMORAL RE/ CELL LINE-SPECIFIC CELL
192 MULTIPLE ANTIGENIC DETERMINANTS ON THE MAJOR
255 RAL REACTIONS IN SYNGENEIC HOSTS AGAINST TUMOR CELL
118 MULATED ONCORNAVIRUS-PRODUCING MOUSE MAMMARY TUM/
65 1) AND THE MURINE MAMMARY TUMOR VIRUS (GP52) ON THE
275 ARY TUMOR VIRUS-INDUCED AND A NORMAL ANTIGEN ON THE
49 VARIATIONS IN THE
89 HOST CELL FACTORS IN THE
85
84 UKEMIA CELLS./
53 LYCOPROTEIN (GP52) ON MOUSE MAMMARY EPITHELIAL CELL
213 AND SHEDDING OF MAMMARY TUMOR VIRUS ANTIGENS ON THE
451 EPIDEMIOLOGY OF CANCER AND HOST

STEROID EXPOSURE ON MAMMARY GLAND DEVELOPMENT AND TUMORIGENESIS
STEROID HORMONES ON VIRUS PRODUCTION. / CONDITIONS F
STEROID INDUCTION OF MOUSE MAMMARY TUMOR VIRUS: EFFECT UPON SYNT
STRAIN AND BREEDING STIMULATION AS FACTORS INFLUENCING THE EFFEC
STRAIN CBA/B1N. / COMPARATIVE INVESTIGATIONS ON MAMMA
STRAIN C3H-AVYFB MICE: NINETY PERCENT INCIDENCE OF MAMMARY TUMO
STRAIN DDD MICE.
STRAIN DDD MICE.
STRAIN GR MICE IN RELATION TO AGE AND TISSUE TYPE.
STRAIN GR MOUSE. / OCCURRENCE AND PRENEOPLASTIC SIGNIFI
STRAIN MICE PERFORMED ON FICOLL GRADIENTS. / BIOLOGICAL ACTIVITY
STRAIN MICE. / MA
STRAIN OF MAMMARY ADENOCARCINOMA: MALIGNANCY, STRUCTURE, VIRAL
STRAIN RIII MICE.
STRAIN SPECIFICITY IN MOUSE MAMMARY TUMOR VIRUS VIRION ANTIGENS.
STRAIN. / BALB/CFRIII
STRAIN. II. GENETIC STUDIES. / TRAN
STRAIN, X/GF. / URE
STRAINS (SHN AND SLN). / TWO-WAY SELECTION OF A STOCK OF SWISS A
STRAINS AND THE DIFFERENT LINES OF THE MAMMARY TUMOR VIRUS.
STRAINS BL/LYDE AND SWR/LYDE MICE.
STRAINS C57BL AND GR: BREEDING TEST OF BACKCROSS SEGREGANTS.
STRAINS OF HIGH AND LOW MAMMARY TUMOR INCIDENCE. / AUTOGE
STRAINS OF MICE. / NEW MORPHOLOGICAL VA
STRAINS OF MICE. II. INHERENT DIFFERENCES BETWEEN THE TWO STRA
STRAINS OF MICE. / IMMUNOLOGY OF THE MOUSE MAMMARY TUMOR VIRUS:
STRAINS OF MOUSE MAMMARY TUMOR VIRUS AS SHOWN BY PARTIAL RNA SEQ
STRAINS RIII AND C3H. / A BIOCHEMICAL APPROACH TO THE STUDY OF T
STRAINS. / TITRATIONS OF VAR
STRAINS. / EXPRESSION OF INDIVIDUAL PROTEINS OF MOUSE MAMMARY G
STRAINS. / DEMONSTRATION BY THE ANTIGLOBULIN CONSUMPTION TEST WI
STRAINS. / DETECTION OF ANTIGENS OF THE MOUSE MAMMARY TUMOR (MTV
STRAINS. / ISOLATION OF THE MOUSE MAMMARY TUMOR VIRUS SEQUENCES
STRAINS. / MECHANISM OF RESISTANCE TO MAMMARY TUMOR DEVELOPMENT
STRAINS. / STUDIES ON ANTIGENIC CROSS-REACTIVITY OF ONCOGENIC RN
STREPTOVARICIN (MEETING ABSTRACT).
STRESS ON BREAST TUMOR INCIDENCE IN MICE.
STRESS ON TUMOR INCIDENCE. (pp. 319-336) / MODIFYING EFFECTS OF
STRESS. / MOUSE MAMMARY TUMO
STRESS, VITAMIN A, AND TUMORS.
STRUCTURAL CHARACTERISTICS OF SOME MURINE RNA TUMOR VIRUSES STUD
STRUCTURAL COMPONENTS OF MOUSE MAMMARY TUMOR VIRUS. I. POLYPEPTI
STRUCTURAL COMPONENTS OF THE MOUSE MAMMARY TUMOR VIRUS: II. VI
STRUCTURAL COMPONENTS OF THE MOUSE MAMMARY TUMOR VIRUS: I. MOR
STRUCTURAL POLYPEPTIDES. (MEETING ABSTRACT). / LOCALIZATION OF
STRUCTURAL STUDIES. / CHARACTERIZATION OF MOUSE MAMMARY TUMOR V
STRUCTURAL, ANTIGENIC, AND BIOLOGICAL CHARACTERISTICS OF PRECANC
STRUCTURE IN THE EXTRACELLULAR STAGES. GENERAL INTERPRETATION O
STRUCTURE OF MOUSE MAMMARY TUMOR VIRUS.
STRUCTURE OF MURINE MAMMARY TUMOUR VIRUSES.
STRUCTURE OF THE MOUSE MAMMARY TUMOR VIRUS: POLYPEPTIDES AND GL
STRUCTURE OF THE MOUSE MAMMARY TUMOR VIRUS: ISOLATION AND CHARAC
STRUCTURE OF THE ONCOGENIC RIBONUCLEIC ACID VIRUSES (ONCORNAVIRU
STRUCTURE OF VIRIONS BUDDING FROM L1210(V) GLN- MOUSE LEUKEMIA C
STRUCTURE. / POLYPEPTIDES OF THE MOUSE MAMMARY TUMOR VIRUS. II.
STRUCTURE, VIRAL PARTICLES. / FIVE-YEAR ANALYSIS
STRUCTURES IN CELL CULTURES OF MOUSE MAMMARY TUMORS. / "DOME
STRUCTURES ISOLATED FROM THE MILK OF INFECTED MICE: MAMMARY TUMO
SUBPOPULATIONS IN THE INDIRECT LEUKOCYTE ADHERENCE INHIBITION AS
SUBSTRAIN OF RIII/DM/SE MICE.
SUBSTRAINS C57BL/M AND C57BL/HE MICE.
SUPPRESSION OF C-TYPE EXPRESSION IN LARGE-SCALE IN VITRO PRODUCT
SUPPRESSION OF SPONTANEOUS TUMORIGENESIS IN MICE.
SUPPRESSOR CELL ACTIVITY IN MICE WITH MUMTV-INDUCED MAMMARY TUMO
SUPPRESSOR CELLS IN MTV-DIRECTED CELLULAR IMMUNITY.
SURFACE COMPONENTS OF HYPOTETRAPLOID ASCITES MAMMARY CARCINOMA C
SURFACE GLYCOPROTEIN OF MURINE MAMMARY TUMOR VIRUSES.
SURFACE INCOMPLETE SACCHARIDE MOIETIES. / HUMO
SURFACE LOCALIZATION OF VIRUS PRODUCTION ON A GLUCOCORTICOID-STI
SURFACE OF MOUSE CELLS. / DETECTION OF THE MAJOR GLYCOPROTEINS O
SURFACE OF MOUSE LEUKEMIA CELLS. / DISTRIBUTION AND ANTIBODY-IND
SURFACE OF MUMTV FROM DIFFERENT SOURCES (MEETING ABSTRACT).
SURFACE OF THE MOUSE MAMMARY TUMOR VIRUS (MEETING ABSTRACT).
SURFACE STRUCTURE OF MOUSE MAMMARY TUMOR VIRUS.
SURFACE STRUCTURE OF VIRIONS BUDDING FROM L1210(V) GLN- MOUSE LE
SURFACE. / IDENTIFICATION OF THE MAMMARY TUMOR VIRUS ENVELOPE G
SURFACES OF GR ASCITES LEUKEMIA CELLS AS COMPARED WITH NORMAL AN
SUSCEPTIBILITY FACTORS: BREAST CANCER. (PP. 49-59)

385 US./ BRIEF COMMUNICATION: IN VITRO
182 INHERITANCE OF
180 HISTOCOMPATIBILITY GENES (THE H-2 COMPLEX) AND
181 HISTOCOMPATIBILITY GENES AND
179 THREE MAMMARY TUMOR VIRUSES IN GENETICALLY SIMILAR
148 O NEW STRAINS (S/ TWO-WAY SELECTION OF A STOCK OF
299 MAMMARY TUMORS IN STRAINS BL/LYDE AND
114 VIRUS. / HORMONE
254 Y CARCINOMA CELLS INDUCING HUMORAL REACTIONS IN THE
255 MOIETIES. / HUMORAL REACTIONS IN
239 MOUSE MAMMARY TUMOR VIRUS (MUMTV)./ REJECTION OF
262 NTISERUM-COMPLEMENT TREATMENT OF TUMOR-CONTAMINATED
252 TUMOR EXTRACTS IN VITRO: EFFECT OF XENOGENEIC AND
208 IN VITRO LYMPHOCYTE SENSITIZATION TO
252 MOR BEARER AND NORMAL MOUSE SPLEEN CELLS TO PHA AND
152 ARY TUMOUR VIRUS IN VITRO. INCREASED MACROMOLECULAR
105 INDUCTION OF MOUSE MAMMARY TUMOR VIRUS: EFFECT UPON
40 ION PREFERENCES FOR POLY(RC).OLIGO(DG)-DIRECTED DNA
16 DNA
37 USE MAMMARY GLAN/ DNA POLYMERASE ACTIVITY AND DNA
102 RODUCTION./ CONDITIONS FOR OPTIMAL MTV
162 DEPENDENT POLYPEPTIDE CHAIN INITIATOR SITES FOR THE
120 LLY-DEFINED MEDIUM. / FACTORS INFLUENCING
194 C ANTIGENS./ SITES OF
104 OF MOUSE MAMMARY TUMOR VIRUS RNA: INCREASED RATE OF
17 D THE EFFECT OF RNA AND PROTEIN INHIBITORS ON VIRAL
397 R CELLS. ABSENCE OF INTERFERENCE BY SIMULTANEOUSLY
164 R CELLS. ABSENCE OF INTERFERENCE BY SIMULTANEOUSLY
24 THE POLYMERASES OF THE ONCOGENIC RNA VIRUSES./
237 THE ROLE OF
257 UNE MECHANISMS AGAINST MAMMARY TUMORS BY INCOMPLETE
256 INHIBITION OF MAMMAF ;UMORS BY INCOMPLETE
197 MEANS FOR THE DETECTION OF TUMOR AND ASSESSMENT OF
286 MODEL SYSTEM FOR EVALUATION OF COMBINED METHODS OF
273 EXPRESSION OF
310 G IN C3HF MICE./ EFFECT OF EARLY
236 NG STIMULATION AS FACTORS INFLUENCING THE EFFECT OF
285 TANEOUS MAMMARY TUMOURS IN MICE. (NEONATAL OR ADULT
234 ORIGENESIS BY MAMMARY TUMOR VIRUS IN THE ABSENCE OF
377 IMMUNOLOGICALLY LABELED WITH TOBACCO MOSAIC VIRUS (
377 SE MAMMARY TUMOR CELLS IMMUNOLOGICALLY LABELED WITH
13 LATENT MAMMARY TUMOR VIRUS./ ANALYSIS OF THE
29 CHARACTERIZATION OF A TERMINAL DEOXYNUCLEOTIDYL
383 CELL
341 ITH BREAST DISEASE./ LYMPHOCYTE
19 ARY TO NUCLEOTIDE SEQUENCES REQUIRED FOR NEOPLASTIC
161 ODODEOXYURIDINE (MEETING ABSTRACT)./
304 THE MURINE MAMMARY GLAND AS A MARKER OF NEOPLASTIC
276 MMARY TUMOR VIRUS ANTIGENS IN MOUSE MAMMARY TUMORS,
10 RCINOMA (MEETING ABSTRACT)./ EVIDENCE FOR
413 MAMMARY TUMOR VIRUS AND HOST GENOME IN THE
396 LB/CF(RIII) MICE. /
395 LB/CFRIII MOUSE./ PRESENCE AND
176 GENETIC
7 I AND/ A BIOCHEMICAL APPROACH TO THE STUDY OF THE
175 II. GENETIC STUDIES./
172 ING ABSTRACT)./ GENETIC
4 TION OF THE MOUSE MAMMARY TUMOR VIRUS SEQUENCES NOT
292 B MICE: NINETY PERCENT INCIDENCE OF MAMMARY TUMORS
290 FATE OF MOUSE MAMMARY TUMOR VIRUS (MMTV)
363 COMPARISON OF THE GROWTH PROPERTIES IN VITRO AND
307 INFLUENCE OF MILK SOURCE ON
302 DI./ SERIAL
130 PARTICLES IN BALB/C MAMMARY NODULE OUTGROWTH LINES
310 EFFECT OF EARLY THYMECTOMY ON GROWTH OF
312 IN BALB/C MICE./ EFFECT OF ERGOCORNINE ON
242 EXTRACTION RESIDUE O/ ACCELERATED DEVELOPMENT OF
112 OF HIGH DOSE OF ESTRADIOL ON THE ICRC MOUSE BEARING
262 T OF TUMOR-CONTAMINATED SYNGENEIC MOUSE BONE MARROW
285 INFLUENCE OF IMMUNOSUPPRESSION ON THE GROWTH OF
63 EFFECT OF
402 MURINE MOP/ RELATIONSHIPS BETWEEN INTRACISTERNAL
408 ETI/ IMMUNOPEROXIDASE STUDIES OF INTRACYTOPLASMIC
349 SPECIFICITY OF HUMAN ANTIBODIES TO INTRACYTOPLASMIC
20 EL SYSTEMS AND NATURAL TISSUE/ PRIMATE AND MURINE
193 PROTEIN OF HIGH- AND LOW-ONCOGENIC MURINE MAMMAR/
393 BIOLOGICAL ACTIVITY OF DIFFERENT ZONES OBTAINED BY
157 PRODUCTION IN CULTURED MOUSE MAMMARY TUMOR CELLS/

SUSCEPTIBILITY OF MINK LUNG CELLS TO THE MOUSE MAMMARY TUMOR VIR
SUSCEPTIBILITY TO ERYTHROCYTE-BORN BITTNER VIRUS IN MICE.
SUSCEPTIBILITY TO MAMMARY TUMOR VIRUS IN MICE.
SUSCEPTIBILITY TO MAMMARY TUMOR VIRUS (MTV) IN MICE.
SUSCEPTIBLE MICE. / COMPARISON OF
SWISS ALBINO MICE FOR MAMMARY TUMORIGENESIS: ESTABLISHMENT OF TW
SWR/LYDE MICE.
SYNERGISM IN THE IN VITRO PRODUCTION OF THE MOUSE MAMMARY TUMOR
SYNGENEIC HOST. / CELL LINE-SPECIFIC CELL SURFACE COMPONENTS OF
SYNGENEIC HOSTS AGAINST TUMOR CELL SURFACE INCOMPLETE SACCHARIDE
SYNGENEIC MAMMARY TUMOR CELLS FOLLOWING IMMUNIZATION WITH KILLED
SYNGENEIC MOUSE BONE MARROW TRANSPLANTS (MEETING ABSTRACT).
SYNGENEIC SERA (MEETING ABSTRACT). / DIFFERENTIAL RESPONSE OF T
SYNGENEIC TARGET CELLS.
SYNGENEIC TUMOR EXTRACTS IN VITRO: EFFECT OF XENOGENEIC AND SYN
SYNTHESES IN MOUSE AND HAMSTER KIDNEY CELLS; PRODUCTION OF B- AN
SYNTHESIS AND DEGRADATION OF VIRAL RNA. / STEROID
SYNTHESIS BY RNA TUMOR VIRUSES AND HUMAN MILK PARTICULATES.
SYNTHESIS BY RNA-CONTAINING TUMOR VIRUSES (MEETING ABSTRACT).
SYNTHESIS IN PRENEOPLASTIC NODULE OUTGROWTH OF BALB/C AND C3H MO
SYNTHESIS IN VITRO AND THE EFFECT OF STEROID HORMONES ON VIRUS P
SYNTHESIS OF DIFFERENT CLASSES OF PROTEINS FOR AN RNA TUMOR VIRU
SYNTHESIS OF MOUSE MAMMARY TUMOR VIRUS BY CELLS GROWN IN CHEMICA
SYNTHESIS OF MURINE RNA TUMOR VIRUS (ONCORNAVIRUS) GROUP-SPECIFI
SYNTHESIS OF VIRAL RNA. / GLUCOCORTICOID-STIMULATED ACCUMULATION
SYNTHESIS. / REPLICATION OF MOUSE MAMMARY TUMOR VIRUS IN TISSUE
SYNTHESIZED MAMMARY TUMOR VIRUS. / FUSION OF XC RAT SARCOMA CELL
SYNTHESIZED MAMMARY TUMOR VIRUS. / FUSION OF XC RAT SARCOMA CELL
SYNTHETIC DNA-RNA HYBRIDS AND RNA-RNA DUPLEXES AS TEMPLATES FOR
T AND SUPPRESSOR CELLS IN MTV-DIRECTED CELLULAR IMMUNITY.
T CELL DEPLETION. / STIMULATION OF IMM
T-CELL DEPLETION.
THERAPY (MEETING ABSTRACT). / MOUSE MAMMARY TUMOR VIRUS ANTIGEN
THERAPY. / SPONTANEOUS MURINE MAMMARY ADENOCARCINOMA:
THY 1 ANTIGEN IN NORMAL AND NEOPLASTIC MAMMARY CELLS OF MICE.
THYMECTOMY ON GROWTH OF TRANSPLANTED MAMMARY GLAND TUMORS ARISIN
THYMECTOMY ON MAMMARY TUMORIGENESIS. / MOUSE STRAIN AND BREEDI
THYMECTOMY/CYCLOPHOSPHAMIDE/WHOLE-BODY IRRADIATION/ALS/VIRUS-FRE
THYMUS, SPLEEN OR BOTH ORGANS. / MOUSE MAMMARY TUM
TMV) (MEETING ABSTRACT). / SCANNING ELECTRON MICROSCOPY (SEM) O
TOBACCO MOSAIC VIRUS (TMV) (MEETING ABSTRACT). / SCANNING ELECT
TRANSFER RNA POPULATION OF MOUSE MAMMARY GLANDS INFECTED WITH A
TRANSFERASE ACTIVITY IN MOUSE MAMMARY TUMOR VIRUS.
TRANSFORMATION AND MOUSE MAMMARY TUMOR VIRUS.
TRANSFORMATION IN VITRO TO RIII MOUSE MILK ANTIGEN AMONG WOMEN W
TRANSFORMATION OF FIBROBLASTS BY AVIAN SARCOMA VIRUSES. / PURIF
TRANSFORMATION OF X/GF MOUSE EMBRYO CELL CULTURES TREATED WITH I
TRANSFORMATION. / ANGIOGENIC CAPACITY OF PRENEOPLASTIC LESIONS O
TRANSFORMED BALB/C MOUSE KIDNEY CELLS, AND GR ASCITES LEUKEMIA C
TRANSLATION OF VIRAL-SPECIFIC RNA IN CELLS OF A MOUSE MAMMARY CA
TRANSMISSION AND CAUSATION OF MAMMARY TUMORS IN MICE.
TRANSMISSION AND EXPRESSION OF THE LEUKEMIA INDUCING AGENT IN BA
TRANSMISSION OF MAMMARY TUMOR VIRUS AND LEUKEMIA VIRUS IN THE BA
TRANSMISSION OF MAMMARY TUMOUR VIRUS BY GR MICE.
TRANSMISSION OF MOUSE MAMMARY TUMOR VIRUSES IN MOUSE STRAINS RII
TRANSMISSION OF THE MAMMARY TUMOR VIRUS BY THE GR MOUSE STRAIN.
TRANSMISSION OF VIRUSES THAT INCITE MAMMARY TUMOR IN MICE (MEET
TRANSMITTED AS GERMINAL PROVIRUS IN THE C3H AND RIII MOUSE STRAI
TRANSMITTED BY EITHER PARENT. / STRAIN C3H-AVYF
TRANSMITTED TO NEWBORN X/GF MICE (MEETING ABSTRACT).
TRANSPLANTABILITY OF CONTINUOUS MOUSE MAMMARY TUMOR CELL LINES A
TRANSPLANTABILITY OF HISTOCOMPATIBLE MAMMARY TUMOURS IN MICE.
TRANSPLANTATION OF URETHAN-TREATED MAMMARY NODULE OUTGROWTH LINE
TRANSPLANTED INTO BALB/CF. C3H AND (C3HF X BALB/C)F1 MICE.
TRANSPLANTED MAMMARY GLAND TUMORS ARISING IN C3HF MICE.
TRANSPLANTED MAMMARY TUMOR GROWTH AND PITUITARY PROLACTIN LEVEL
TRANSPLANTED MAMMARY TUMORS IN MICE PRETREATED WITH THE METHANOL
TRANSPLANTED MAMMARY TUMORS. / INFLUENCE
TRANSPLANTS (MEETING ABSTRACT). / ANTISERUM-COMPLEMENT TREATMEN
TRANSPLANTS OF SPONTANEOUS MAMMARY TUMOURS IN MICE. (NEONATAL OR
TRYPSIN ON MOUSE MAMMARY TUMOR VIRUS.
TYPE A AND EXTRACELLULAR ONCORNAVIRUS-LIKE PARTICLES PRODUCED IN
TYPE A PARTICLES IN MOUSE MAMMARY TUMOR TISSUE CULTURE CELLS (ME
TYPE-A PARTICLES OF THE MURINE MAMMARY TUMOR VIRUS. /
TYPE-C VIRAL NUCLEIC ACID ASSOCIATION KINETICS: ANALYSIS OF MOD
TYPE-SPECIFIC ANTIGENIC DETERMINANTS ON THE MAJOR EXTERNAL GLYCO
ULTRACENTRIFUGATION OF THE LACTEOUS FACTOR FROM PS STRAIN MICE P
ULTRASTRUCTURAL AND QUANTITATIVE STUDIES OF MAMMARY TUMOR VIRUS

94 RY CARCINOMA WITH FOUR ONCOGENIC RNA VIRUSES (M/ ULTRASTRUCTURAL COMPARISON OF A VIRUS FROM A RHESUS-MONKEY MAMMA
311 TARGET ORGAN FOR A SYSTEMIC EFFECT OF ULTRAVIOLET RADIATION.
165 /GF./ URETHAN AND X-RAY EFFECTS ON MICE OF A TUMOR-RESISTANT STRAIN, X
302 SERIAL TRANSPLANTATION OF URETHAN-TREATED MAMMARY NODULE OUTGROWTH LINE D1.
132 BESTROL IN THE MOUSE. (MEETING ABSTRACT)./ UTERINE, VAGINAL, AND PROLACTIN RESPONSES TO DIETARY DIETHYLSTIL
132 N THE MOUSE. (MEETING ABSTRACT)./ UTERINE, VAGINAL, AND PROLACTIN RESPONSES TO DIETARY DIETHYLSTILBESTROL I
69 MICE. / NEW MORPHOLOGICAL VARIANTS OF MOUSE MAMMARY TUMOUR VIRUS IN HIGH TUMOUR STRAINS OF
8 IC ACID SEQUENCES BETWEEN MOUSE MAMMARY TUMOR VIRUS VARIANTS. / RELATIONSHIP IN NUCLE
151 HIGH FREQUENCY VARIATION IN MAMMARY TUMOR VIRUS EXPRESSION IN CELL CULTURE.
106 HIGH FREQUENCY VARIATION IN MAMMARY TUMOR VIRUS EXPRESSION IN CELL CULTURE.
122 OR-DERIVED CELL CLONES./ VARIATIONS IN PHENOTYPIC EXPRESSION OF MMTV IN MOUSE MAMMARY TUM
49 ING ABSTRACT)./ VARIATIONS IN THE SURFACE OF MUMTV FROM DIFFERENT SOURCES (MEET
210 RINE MAMMARY TUMOR VIRUS./ PSEUDOTYPES OF VESICULAR STOMATITIS VIRUS WITH ENVELOPE ANTIGENS PROVIDED BY MU
283 ACTINOMYCIN D AND X-RADIATION SUPPRESSION OF SPONTANEOUS TUMORIGENESIS IN MICE.
165 URETHAN AND X-RAY EFFECTS ON MICE OF A TUMOR-RESISTANT STRAIN, X/GF.
290 E MAMMARY TUMOR VIRUS (MMTV) TRANSMITTED TO NEWBORN X/GF MICE (MEETING ABSTRACT). / FATE OF MOUS
223 CHARACTERIZATION OF X/GF MICE WITH RESPECT TO THEIR RESISTANCE TO ONCOGENESIS.
291 MAMMARY CARCINOGENESIS IN FOSTER-NURSED X/GF MICE.
161 MEETING ABSTRACT)./ TRANSFORMATION OF X/GF MOUSE EMBRYO CELL CULTURES TREATED WITH IODODEOXYURIDINE (
165 X-RAY EFFECTS ON MICE OF A TUMOR-RESISTANT STRAIN, X/GF. / URETHAN AND
164 MOUSE MAMMARY TUMOUR CELLS. ABSENCE O/ FUSION OF XC RAT SARCOMA CELLS INDUCED BY MURINE LEUKAEMIA VIRUS-INFECTED
397 MOUSE MAMMARY TUMOUR CELLS. ABSENCE O/ FUSION OF XC RAT SARCOMA CELLS INDUCED BY MURINE LEUKAEMIA VIRUS-INFECTED
252 A AND SYNGENEIC TUMOR EXTRACTS IN VITRO: EFFECT OF XENOGENEIC AND SYNGENEIC SERA (MEETING ABSTRACT). / DIFFERENTIA
303 Y TISS/ NEOVASCULARIZATION INDUCED BY INTRAOCULAR XENOGRAFTS OF NORMAL, PRENEOPLASTIC, AND NEOPLASTIC MOUSE MAMMAR
74 UMOR VIRUS (MTV) IN DIFFERENT GRADIENT/ ISOPYCNIC ZONAL CENTRIFUGATION AND CHARACTERIZATION OF THE MOUSE MAMMARY T

AUTHOR INDEX WITH CITATION NUMBERS

Aaronson SA.....16, 41, 44
Aarssen AM.....394
Abeloff MD.....459
Abenova UA.....346
Abraham S.....272
Adelberg M.....281
Adelberg MG.....240
Aidells BD.....300
Aldrich CD.....205
Andervont HB.....293
Arthur LO116, 118, 122, 125, 212, 376
Ashley RL.....29, 31, 114
Attia AB.....357
Axel R10, 21, 38, 320, 328, 329, 333, 444, 445
Bailey DW.....183
Baker RR.....459
Baldi A.....189
Baltimore D.....26
Banerjee MR36, 37, 373, 374, 375
Bauer H.....353
Bauer RF.....121, 376
Baxt W.....321, 328, 445
Benton CV.....117
Bentvelzen P9, 72, 99, 172, 196, 214, 237, 271, 315, 394, 415, 420, 441
BenShaul Y.....159
Bern HA.....135, 374
Berzinski R.....211
Bishop JM5, 6, 11, 15, 19, 76, 100, 104, 438
Bistocchi M.....141
Black MM317, 318, 330, 334, 335, 343, 355, 356, 446
Blackman KE.....270
Blair PB6, 74, 199, 200, 201, 224, 226, 227, 228, 229, 230, 231, 233, 249, 250, 256, 257, 266, 278, 337
Blumenschein G...344, 351
Boehm-Truitt M.....365
Bolis GB147, 178, 235, 236, 395, 396
Bolognesi DP..65, 93, 340
Bonhag RS.....266
Bont WS.....275
Borden EC.....459
Bowen J.....344, 351
Bowen JM...338, 339, 361
Brendler T.....402
Brennan MJ.....312
Brinkhof J.....72
Brooks RE.....282
Brown BL.....121
Brown J.....134
Brown R.....270
Bucciarelli E.147, 395, 396
Buck CA.....54
Buijs F.....152, 160, 276
Burki HR.....391
Burny A.....21, 24
Butel JS.....363
Bykovsky AF83, 346, 358, 359, 360
Calabresi P.....265, 267
Calafat J101, 152, 160, 172, 196, 206, 213, 271, 274, 276
Calberg-Bacq CM.....62
Calvelli TA.....84
Came PE.....170, 268, 287
Cammoun M.....357
Cardiff RD.....2, 29, 114, 61, 74, 88, 186, 337, 371, 389, 430
Carter DP.....377
Ceriani RL.....272
Cernosek SF.....132
Charney J64, 71, 73, 75, 77, 185, 239, 248, 289, 348, 439, 456
Chen PL.....68, 163
Chianale C.....171
Cho JR.....332
Chopra HC.....69
Clark JH.....305
Cleveland G.....95
Cody CM.....239, 248
Cohen D.....240, 241
Colcher D4, 25, 43, 78, 82, 322, 366, 416, 455
Colcher DM.....381
Cole P.....452
Colley VB.....130
Compans RW.....55
Coriell LL.....32
Creemers P..190, 214, 237
Cuatico W.....332
Culbreth K.....93
Cunningham-Rund341, 341
Daams JH99, 172, 196, 222, 271, 353
Daly T.....184
Daly TM.....49, 50, 63, 89
Damsky CH.....51, 52
Daniel CW.....300
Danilovs JA.....173
Das MR.....24
Davin ER.....284
Dawson PJ.....282
De Maeyer-Guign.....183
De Mayer E.....183
De Moes J.....176
Dean JH.....352
Deinhardt F.....421
Deinhardt JB.....421
Dejak D.....331
Delage G.....171
Demsey A.....84, 91
Deringer MK.....299
Dexter DL.....364
DeOme KB103, 129, 130, 297, 298
Dickson C34, 59, 102, 108, 210
Dion A.....123, 330
Dion AS3, 17, 28, 32, 33, 40, 57, 58, 64, 184, 317, 318, 362, 387, 439
Djaziri M.....357
Dmochowki L.....209
Dmochowski L.....79, 202, 338, 339, 361, 409
Dobbertin DC.....402
Dodson ML.....338
Dorfler W.....326
Drohan W...4, 25, 82, 416
Duafala JC.....90
Dudley JP.....363
Dunn TB.....293
Dupont B.....341
Dutrillaux MC.....86
Dutrillaux-Ducr.....87
Dux A.....144, 180, 181
Economou JS.....238, 262
Egawa K.....254, 255
El-Fiky SM.....12
Emmelot P.....275
Farmer JH.....133
Fasske E.....404
Faulkin LJ.....129
Feldman S.....428, 455
Feldman SP.....323
Feller WF.....341
Fetting R.....404
Fieldsteel AH.....282
Fine DL116, 118, 121, 122, 124, 125, 127, 212, 376
Fligiel Z.....364
Fout GS.....32, 33, 40
Francois C.....62
Friedrich R.....5
Fugmann RA284, 286, 314
Fujinaga S.....209
Furmanski P 342, 433, 453
Gantt R.....39
Garzon S.....204
Gass GH.....134
Gates O.....295
Gelderblom H.....353
Ghosh AK.....291
Gilden R.....20
Gilden RV.....211
Gilead Z.....159
Gillespie D.....322
Gillespie S.....322
Gillette RW113, 218, 232, 270, 273
Gimbrone MA.....303, 304
Glancy T.....319
Goldberg RJ.....106, 151
Goldfeder A.....161, 165, 223, 290, 291
Golubev DB.....83
Gonda MA.....118
Good RA.....341
Goodman HM.....5
Gorka C.....46, 167
Gorka G.....166
Gosselin L.....62
Grant P.....342
Grant PM.....319
Greene AE.....387
Greenman DL.....132
Griswold D.....267
Griswold DE.....265, 269
Grossmann H80, 216, 347, 350, 414
Gruntenko EV.....285
Gulati S.....21
Gulati SC.....38, 333
Gullino PM.....303, 304
Guntaka RV.....19
Gutierrez-Cerno.....132
Haber M.....241
Hackett AJ.....74
Hageman P.....9, 172, 196
Hageman PC206, 213, 222, 276, 410, 425
Hageman PH.....187
Hall WT.....183
Halmi L.....312
Hamamoto ST.....90
Harter DH.....21
Hartman JR.....159
Haslam S70, 102, 136, 182, 205
Hatanaka M.....20
Haverman J.....275
Hayden ML.....238
Hayworth PE.....284, 314
Hazlewood CF.....95
Heberling RL.....403
Hehlmann R...9, 321, 329
Heine UI.....3
Hekman A.....276
Helmich C70, 136, 168, 175, 182
Helmke RJ.....403
Henry M.....81, 86, 87, 264, 392
Hentzen D.....13
Heppner G.....267
Heppner GH208, 265, 269, 364, 447, 450
Herberman RB....352, 454
Hersh E.....344
Heston WE149, 153, 169, 292, 413, 422, 442
Heubel G.....119, 382
Highman B.....133
Hilgers J48, 101, 177, 202, 213, 274, 275, 276, 441
Hilgers JH.....195
Hillman EA.....122, 125
Hiraki S.....409
Holben JA.....75, 77, 239, 248
Holder WD.....65, 340
Hollande E 81, 86, 87, 392
Hollmann KH423, 424, 440

Hollmann MK.....462
Holmes EC.....203
Hor'no M.....408
Houw ing A.....394
How- J DK.....78, 381
Howk RS.....35
Hu R.....331
Hubbell ES.....106, 151
Humphrey LJ.....448
Hutchison DJ.....68
Ihle JN.....212
Ikeda H.....194
Ilyin KV83, 346, 358, 359, 360
Imai M.....408
Iramain CA.....305
Irlin IS.....83, 346, 358
Jackson B.....344
Jackson N.....15, 76
Jacobs DM.....242
Jennings BR.....283
Johnson RJ.....238
Jouanne C.....81
Julian BT.....39
Kacian D.....43
Kaizer H.....262
Kalter SS.....403
Kaplan HS.....67
Kawakami T.....20
Kawka D.....84, 91
Kelley SP.....124, 125, 127
Kemmer C277, 280, 349, 350, 414
Kersey JH.....247
Kettmann R.....4, 82
Keydar J.....24, 159
Kieler J.....309
Killeen LA.....35
Kim U.....131
Kimball P.....66, 416
Kimball PC.....365, 366
Kisielow P.....279
Klahr G.....221
Klein PA.....429
Kohne D.....20
Kopp JS.....269
Korb J.....3
Kortright KH.....312
Kowalski HM.....364
Kozikowski EH.....126
Kramarsky B68, 73, 94, 156, 157, 158, 163, 271, 296, 368, 388, 439
Krawczynski K.....279
Kripke ML..242, 266, 311
Kryukova IN.....198
Kufe D9, 192, 193, 328, 329, 445
Kurahara C.....282
Kwa HG.....187
Lacour F.....171
Laing CA.....252, 259
Lambre C.....204, 264
Lane MA227, 228, 229, 230, 231, 233, 250, 257
Lappe MA.....266
Lasfargues EV.....460
Lasfargues EY89, 100, 119, 123, 156, 157, 158, 271, 368, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 439
Lasfargues JC119, 123, 158, 368, 378, 382, 383, 384, 385, 386, 387, 388
Laufs R.....42, 326
Lavrin DH.....263
Lavrovsky VA.....198
Lee BK.....400, 401
Leis HP.....335, 343, 355
Levinson WE.....15, 76
Liebes L.....96, 97, 98
Lin FK.....373
Links J115, 152, 160, 164, 276, 397
Litwack M.....406
Lloyd EL.....150
Lo Gerfo P.....345
Lo-Gerfo P.....185
London WT.....451
Long A.....336
Long CW.....211
Longfellow DG....405, 406
Longley C.....342
Lopez DM...191, 215, 260
Lossnitzer A.....221
Loutit JF.....150
Lowery LT.....218, 232
Lozinksy TF.....83
Lozinsky TF.....358
Luftig RB.....93, 96, 98
Lund JK.....88
Mackevicius F.....150
Manning JS29, 31, 74, 269
Manthey WJ.....92, 296
Mar P.....227, 228
Marcus SL.....27, 30
Marineau EJ.....14
Martin DS197, 284, 286, 294, 314
Maruyama K.....338
Marx JL.....461
Mason JM.....283
Matsuzawa A145, 146, 308
May-Levin F.....458
Mcgrath CM.....342
McCormick J.....453
McCormick JJ96, 97, 98, 433
McCoy J.....352
McGrath CM14, 155, 319, 336, 369, 370, 371, 412, 433, 453
McMillan PN.....93
Medeiros E.....15, 76, 438
Medina D95, 103, 129, 130, 220, 297, 298, 302, 305, 306, 316, 363, 417, 419
Mehta RG.....27, 374
Meites J.....312
Mekori T.....240
Mel HC.....74
Meyers P.....260
Michael B.....350
Michalides R7, 8, 9, 82, 366, 416, 428, 455
Micheel B.....277, 449
Miller G.....431
Miller GG.....83, 346, 358, 360
Miller MF.....338
Mills KT.....135
Mistry P.....166
Miyamoto MJ.....143
Mizutani S.....26
Modak MJ.....27, 30
Molling K.....353
Moore DH1, 12, 22, 28, 32, 33, 48, 64, 68, 71, 73, 75, 77, 85, 94, 119, 123, 156, 157, 158, 163, 170, 239, 248, 268, 287, 288, 289, 317, 318, 325, 335, 343, 348, 368, 378, 382, 384, 385, 386, 387, 388, 427, 432, 439, 456, 457
Moore HD.....460
Moore J.....309
Moore SH.....47
Mori T.....135
Morris VL.....5
Mortensen RF.....225
Morton DL.....203
Moulton A.....345
Mourali N.....357
Mouriguand MC.....166
Mouriquand C.....393
Mouriquand J166, 167, 393
Mueller M.....350
Muhlbock O180, 181, 411, 425
Mukherjee AS.....36
Muller M80, 216, 217, 219, 222, 277, 280, 347, 349, 407, 414
Myers B.....202, 209
Nagasawa H.....148
Nagashima K.....118
Nagle SC.....120
Nakahara W.....148
Nandi S.....18, 53, 59, 70 102, 128, 136, 174, 175, 182, 205, 412 155, 168,
Nemanic MK.....377
Newgard KW.....337
Noon MC.....60
Nooter K.....315
Norvell MJ.....133
Nouwen T.....101, 274
Nowinski RC11, 22, 47, 48
Nusse R.....275
O'Neill FJ.....106, 151
O'Reilly R.....341
Ohno T.....43, 331
Okabe H.....20
Okey AB.....134
Okita GT.....391
Old LJ.....48
Olivi M.....236
Orme LA.....121
Ortiz-Muniz G.....191, 215
Osterrieth PM.....62
Oth D.....307
Pai SR.....112
Parks W.....20, 354
Parks WP35, 44, 60, 105, 106, 107, 109, 110, 126, 151, 153, 154, 413
Pasternack GR.....238
Pattengale PK.....194
Peer GW.....65, 340
Peterson JA.....272
Pillsbury N.....158, 378
Pitelka DR.....90, 130, 313
Plowman JK122, 124, 125, 127
Pomenti AA....17, 58, 362
Ponenti A.....3
Postuma HS.....251
Priori ES.....338
Prop FJ.....372
Puentes MJ.....61
Pullinger BD.....289
Puma JP.....59
Quintrell N.....15, 76, 438
Radzikowski C....279, 309
Ranadive KJ.....409
Rands E.....41
Ransom JC.....109
Razvorotnev VA.....198
Rentier-Delrue.....62
Retzel E.....98
Ribacchi R.....301
Rich M.....98
Rich MA97, 319, 336, 342, 433, 453
Riley V.....137, 139, 140
Rimai L.....96, 97, 98
Ringold G.....109
Ringold GM6, 104, 111, 389, 390
Rios A243, 244, 245, 246, 247, 253
Ritter RI.....136
Ritzi E.....189, 294
Ritzi EM.....197
Robertson DL.....402
Robertson S.....270
Robinson B.....351
Robinson CS.....383
Robinson E.....240, 241
Robinson OR.....117
Ross J.....44
Rossi G.....178
Roubinian J.....233
Roubinian JR.....256, 257
Rowson KE.....437
Rudczynski AB.....225
Ruhland D.....404
Russell A.....45
Russo J.....433, 453
Rye LA.....35
Sabolovic D.....307
Saito M.....254
Salmeen I.....96, 97, 98
Santisteban G.....140
Santos GW.....262
Sarkar NH' 11, 12, 17, 22, 27, 30, 47, 48, 57, 58, 64, 68, 71, 73, 84, 85, 92, 94, 158, 362, 368, 439
Save PG.....112
Scanlon M.....339
Schafer W.....353
Scheer DI.....48
Schidlovsky G.....117
Schloemer RH.....66
Schlom J4, 7, 8, 9, 10, 24, 25, 43, 66, 78, 82, 162, 192, 193, 320, 322, 323, 324, 325, 328, 329, 365, 366, 381, 416, 428, 445, 455
Schochetman G66, 162, 365, 416, 434, 455
Scholm J.....21
Schorr I.....45
Scolnick E.....41
Scolnick EM16, 20, 35, 44, 105, 106, 107, 109, 110, 126, 151, 154
Segev Y.....281
Seifter E.....138
Seman G.....338, 339, 361
Shank PR.....390
Shannon JM.....300
Sheffield JB49, 50, 51, 52, 54, 63, 89, 92, 184, 379
Shellenberger T.....133
Shibley GP.....117
Shigematsu T.....79
Shih TY.....105
Shin HS.....238, 262
Shore B330, 334, 335, 343, 355
Shyamala G.....108
Sigel MM....191, 215, 260

Silverstein G.....185, 345
Simmons RL243, 244, 245, 246, 247, 253
Singh DV 312
Slomich M.....233, 257
Sluyser M 101, 274
Smith B.....153
Smith GC 403
Smith GH39, 149, 200, 292, 293, 398, 399, 400, 401, 405, 406
Smith RT 429
Souissi T 357
Soule H.....342, 453
Soule HD 319, 336
Spackman D 137, 140
Spiegelman S9, 10, 21, 23, 24, 38, 43, 189, 197, 294, 320, 321, 322, 323, 324, 325, 327, 328, 329, 331, 332, 333, 428, 435, 436, 443, 444, 445, 455
Spure ZZ.....346
Squartini F.....141, 234, 235, 236, 395, 396 147, 178,
Stackpole CW.....84, 91
Stadler U.....161
Stehelin D.....19
Steinke H 42, 326
Steuden J.....279
Stolfi RL197, 286, 294, 314
Stutman O207, 258, 261, 454
Suciu-Foca N 345
Sulitzeanu A.....281
Sullivan M 344
Suzuki K 145, 146, 308
Svec J 115, 164, 397
Swearingen GR.....209
Sweeney TK 402
Sweet RW.....331
Szkudlarek J.....279
Tabbane F 357
Tanaka H 56
Tang R 53
Taniguchi H.....48
Tanino T 254, 255
Taraschi N.49, 63, 89 184
Taraschi NE.....58
Temin HM.....26, 418
Teramoto YA2, 61, 78, 88, 192, 193, 381
Thach RE.....402
Thach SS.....402
Themann H.....404
Theuns GJ 195, 275
Thomas JA81, 86, 87, 204, 264, 392
Thorbeck GJ 194
Todaro GJ.....16, 41, 44
Tokuzen R.....148
Tol O.....152, 160
Travnicek M 24
Trefts P.....233
Trites P 246
Tuszynski GP 52
Ulrich K.....309
Vaage J 220
Vaidya A 380
Vaidya AB33, 40, 119, 317, 318, 382, 385, 386
Van der Gugten 188
Van Blitterswij.....213, 275
Van Nie R.....176
Van Nie RV.....195
Van NIE R.....177
Van Pelt FG 394
Varmus HE5, 6, 11, 15, 19, 76, 100, 104, 389, 390, 438
Verbeet M 213
Verley JM.....423
Verstraeten AA....176, 187
Viala C 393
Videlets IY.....310
Vilain C 86, 392
Visser AS.....372
Vlahakis G7, 69, 82, 142, 149, 169, 179, 292
Vokaer A.....426
Volkova MY 83, 358
Voyles BA 14, 370
Wagner H.....80
Wagner JE.....37
Wagner RR.....66
Wanebo H 341
Warren L.....51, 52, 54
Warren S.....295
Washburn LL.....374, 375
Watson K 24
Watson KF.....353
Weber GH 3
Wei WZ 208
Weiss DW200, 240, 241, 281
Weiss R.....210
Weissman IL 67
Wells SA 65, 340
Williams CJ 28
Williams WC..79, 202, 209
Wiseman C 344, 351
Witkin S.....43
Witte ON 67
Wivel NA 398
Wolford RG.....60
Wood BG 375
Woodside N 69
Yagi MJ55, 90, 229, 231, 367
Yamamoto KR104, 389, 390
Yamamoto T145, 146, 308
Yanai R 148
Yang J 53, 128
Yaniv A 43
Yau P 402
Yershov FI 360
Young HA...105, 107, 110
Young J 82, 455
Young JM 78, 381
Young L.....103, 155, 266, 281
Young LJ61, 114, 116, 371
Young PN 135, 374
Yron I 240, 241
Zacharchuk CM.....63
Zachrau RE330, 334, 335, 343, 355
Zavada J 210
Zeve VH.....118
Zhdanov VM83, 346, 358, 359, 360
Zotter S80, 216, 217, 219, 221, 280, 349, 350, 407, 414
Zotter ST277